# The American Journal of Medicine



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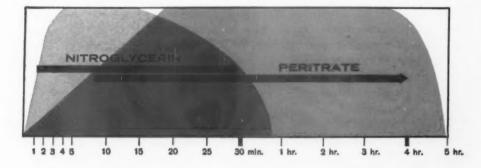
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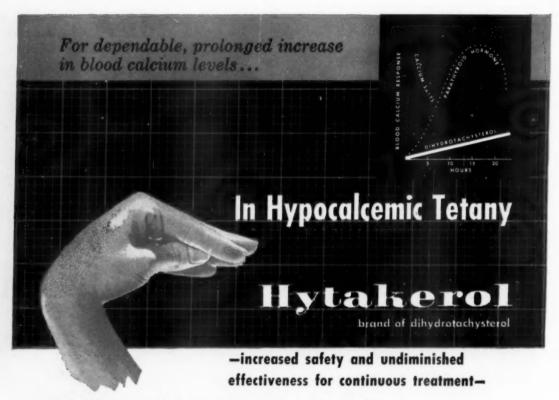
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hypocalcemic tetany."<sup>2</sup>

Winthrop LABORATORIES NEW YORK 18, N. Y.

- Grollman, Arthur: Essentials of Endocrinology. Philadelphia, J.B. Lippincott Co., 2nd ed., 1947, p. 269.
- Sandock, Isadore: Tetany and ovarian function. J.A.M.A., 160:659, Feb. 25, 1956.

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Tonic contraction of the facial muscles results from tapping the facial nerve as it issues from the stylomastoid foramen—one of the diagnostic indications of hypocalcemic tetany.



### The American Journal of Medicine

Vol. XXIV JUNE, 1958 No. 6

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# Editorial Clinical Electrocardiography at the Crossroads . . . . . . Arthur Selzer 831 Clinical Studies

Tricuspid Stenosis. Clinical Features in Twelve Cases
Thomas Killip, III and Daniel S. Lukas 836

The clinical diagnosis of tricuspid stenosis has always been uncertain, in part because of the usual association with mitral valvulitis, in part because the conventional criteria are often unreliable as is clearly brought out. In twelve cases the authors noted, as the most characteristic clinical feature, a diastolic murmur and thrill in the third to fifth intercostal space to the *left* of the sternum—this location is convincingly accounted for—which, unlike mitral murmurs, increase in intensity with inspiration and decrease with expiration. The associated clinical, fluoroscopic, electrocardiographic and catheterization findings are described, none altogether characteristic but together permitting the diagnosis with more confidence than previously justified. Among other points of interest discussed are the apparent "protective" action of tricuspid valve obstruction, the enhanced propensity to edema formation, and the occasional development of "giant" right atrium. All in all, the paper provides a well balanced discussion which is both interesting and informative.

Estimation of Severity of Aortic Stenosis by Combined Heart Catheterization
HARRY GOLDBERG, RALPH C. SMITH AND GEORGE RABER 853

The usefulness of left- and right-sided (combined) cardiac catheterization in evaluating the severity of aortic stenosis is demonstrated in this study of thirty-seven cases. The characteristic changes in cardiac output, pressure gradient across the aortic valve, left ventricular work and end diastolic pressure are described. Calculation of the aortic valve area indicates that if less than a critical size. 1.0 cm., manifestations of aortic stenosis are apt to appear.

The Phonocardiogram in Mitral Valvular Disease. A Correlation of Q-1 and 2-OS Intervals with Findings at Catheterization of the Left Side of the Heart and at Mitral Valvuloplasty

Munro H. Proctor, Rhett P. Walker, Ernest W. Hancock and Walter H. Abelmann 86

In this careful study the quantitative features of the phonocardiogram in mitral stenosis were correlated with the findings at left heart catheterization and operation in forty-nine patients with mitral valvular disease. In patients with demonstrated mitral stenosis the Q-1 interval usually was

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#### **AN AMES CLINIQUICK**

CLINICAL BRIEFS FOR MODERN PRACTICE



#### is there any correlation between the amount of protein in urine and the grade of heart failure?

Yes. There is a fairly positive correlation.

Source-Race, G. A.; Scheifley, C. H., and Edwards, J. E.: Circulation 13:329, 1956.

#### Proteinuria In Cardiac Failure

Grade	Mg. % Protein										
Orace	0	10	20	30	40	50	60	70	80	90	100
I (31 patients)	8 patie	nts	23 p	atient	s	<b>→</b>					
IV (11 patients)				7	patien	ts -	+	3 pa	tients	$\rightarrow$	† patient

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prolonged but there was poor correlation with mitral aperture size, left atrial mean pressure, and the end-diastolic pressure gradient across the mitral valve. In contrast, there was a significant correlation between the 2-OS interval and left atrial mean pressure, independent of the valve size. The findings in patients with mitral insufficiency, alone and in combination with mitral stenosis, also are presented. The authors conclude that the quantitative features of phonocardiography may provide useful information in the evaluation of mitral valvular disease but their value is limited and cannot substitute for direct hemodynamic studies in problem cases.

The Effect of Mephentermine Sulfate on Myocardial Oxygen Consumption, Myocardial Efficiency and Peripheral Vascular Resistance

GEORGE H. WELCH, JR., EUGENE BRAUNWALD, R. B. CASE AND STANLEY J. SARNOFF

In this model study it is shown convincingly in the dog that mephentermine sulfate, widely employed in shock states to restore circulatory dynamics, exerts relatively little influence on total peripheral vascular resistance (despite its common usage to effect an increase) but produces a marked elevation of the ventricular function curve. When the heart was not dilated, the drug produced an increase in oxygen consumption and a decrease in external efficiency; however, when the filling pressure was at high levels, reverse effects were obtained.

The Changes in Concentration of Cholesterol in the Serum of Hypertensive Patients
During Antihypertensive Therapy

Q. B. Deming, M. E. Hodes, A. Baltazar, J. G. Edreira and Seta Torosdag 882

Some antihypertensive regimens, such as the rice diet, hydralazine administration and ganglionic blockade, also cause a decrease in serum cholesterol in most instances. The authors are much impressed by this general parallelism of effects and suspect a common mechanism. A cause and effect relationship is not demonstrated, however, and a common mechanism, if indeed one exists, is not established.

Exaggerated Natriuresis in Essential Hypertension

DAVID S. BALDWIN, ALBERT W. BIGGS, WILLIAM GOLDRING, WILLIAM H. HULET AND HERBERT CHASIS 893

This experimental study confirms previous reports indicating that while the basal urinary sodium excretion of hypertensive patients is equivalent to that of normotensive subjects on comparable diets, they excrete sodium excessively in the urine when infused with hypertonic saline solution under specified conditions. By varying the circumstances of the experiment, the present investigators further demonstrate that the observed differences probably are not referable to impairment of tubular reabsorption of sodium in the hypertensive patients studied, to increase in filtered sodium load due to enhanced glomerular filtration rate as a result of the infusion, or to other discernible intrinsic renal factors. They conclude, therefore, that some as yet undefined extrarenal mechanism is responsible.

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### EASIER CONTROL OF SUMMER-TIME ALLERGIES

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aw Organon development ORGANON INC. · ORANGE, N. J.

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VOLUME TWENTY-FOUR

NUMBER SIX

#### Carcinoid Syndrome Produced by Metastasizing Bronchial Adenoma RICHARD R. PICHEL WARNER AND A. LOUIS SOUTHREN 903

In a report of unusual interest, the carcinoid syndrome in two cases was found in association with a metastasizing bronchial adenoma. It has long been appreciated that some bronchial adenomas morphologically resemble carcinoid tumors of the gastrointestinal tract but excessive serotonin secretion by bronchial adenomas has not hitherto been demonstrated.

#### Reviews

#### New Concepts in the Evaluation of Intersex and Infertility

This paper deals with the discovery of "chromatin sex" and application of this interesting development to clinical problems of intersex and infertility. The authors have employed the leukocyte as a readily accessible somatic cell for sex differentiation. Chromatin-positive cells, which exhibit a typical "drumstick," denote female sex; chromatin-negative cells, devoid of "drumsticks," denote male sex. The implications of expected but sometimes of paradoxical sex in diagnosis and management of such conditions as gonadal aplasia, gonadal dysgenesis, Klinefelter's syndrome, adrenogenital syndrome and hermaphroditism are illustrated by representative case problems.

DONALD K. BRIGGS AND HERBERT S. KUPPERMAN

### Physical Therapeutic Measures in the Treatment of Chronic Bronchopulmonary Disorders. Methods for Breathing Training . . . . WILLIAM F. MILLER 929

The usefulness of physical measures in the management of chronic bronchopulmonary disease is reemphasized. Dr. Miller gives a critical discussion of the underlying theory, aims and methods, and outlines his methods of procedure. Of importance is muscle relaxation, a slow pattern of breathing with emphasis on expiration both at rest and on exercise. Such additional aids as proper use of nebulizer therapy, postural drainage and efficient methods of coughing are described. Adjuvant methods include the use of abdominal belts and institution of pneumoperitoneum.

#### Seminar on Liver Disease

#### The Surgery of Portal Cirrhosis of the Liver . . . . . Robert R. Linton 941

Dr. Linton closes the seminars on liver disease with an analysis of his experience with the surgical management of bleeding varices in portal cirrhosis. If hemorrhage is so brisk as to require balloon tamponage, he recommends that this procedure be followed immediately by emergency transthoracoesophageal suture of the bleeding varices. It has been possible in this way to avoid further hemorrhage long enough to prepare the patient more adequately for definitive shunt surgery. Dr. Linton prefers splenorenal vein anastomosis, but whether splenorenal or direct portacaval shunt is performed, the follow-up data convincingly demonstrate prolongation of the life of the cirrhotic patient with esophageal varices that have bled, and reduction in the incidence of recurrent hemorrhage.

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FIRST—clinically confirmed for better management of psychotic patients

NOW-clinically confirmed as an improved antiemetic agent



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Clinical investigators\* report that in clinical studies

Post- operatively	After Nitrogen Mustard Therapy	In Chronic Nausea and Vomiting	In Infections, Intra-abdominal Disease, and Carcinomatosis	In Neurosurgical Diagnostic Procedures	In Pregnancy When Vomiting is Persistent
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\*Reports to the Squibb Institute for Medical Research

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992

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Alcoholism, Diarrhea, Osteoarthropathy, Hepatomegaly, Fever and Sudden Death. Clinico-pathologic Conference (Washington University School of Medicine).	948
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The Absorption of Fats, Studied in a Patient with Chyluria ROLF BLOMSTRAND, NEILS A. THORN AND E. H. AHRENS, JR.	958
The authors made full use of the opportunities afforded by a case of chyluria. After a careful analysis of the mechanism of the chyluria they were able to stop the loss of chyle by the simple device of increasing intra-abdominal pressure by means of a corset. Elegant studies on fat absorption also were carried out; these confirm and extend current views in respect to routes of absorption of shortand long-chain fatty acids.	
Acquired Fibrinogenopenia	967
Two interesting examples of this increasingly reported condition are recorded, one in a patient with extensive amyloidosis of the liver, the other in the more familiar setting of pregnancy with intrauterine fetal death occurring many weeks before delivery.	
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A well studied case of unusual interest.	
Cushing's Syndrome and Bronchogenic Carcinoma RENATO D. KOVACH AND LAURENCE H. KYLE	981
This is an interesting association, as the authors point out, and may be responsible for unusual and puzzling symptoms and signs. For these, explanations are offered which, even if a point is stretched here and there, are certainly plausible.	
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# Arrest the anxiety factor in heart disease

without affecting autonomic function

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\* Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.

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REFERENCES: (1) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: Canad. M.A.J. 77:844 (Nov. 1) 1957. (2) Schneierson, S. S.: J. Mt. Sinai Hosp. 25:52 (Jan.-Feb.) 1958. (3) Hasenclever, H. F.: J. Iowa M. Soc. 47:136, 1957. (4) Rhoads, P. S.: Postgrad. Med. 21:563, 1957. (5) Caswell, H. T., and others: Surg. Gynec. & Obst. 106:1, 1958. (6) Josephson, J. E., & Butler, R. W.: Canad. M.A.J. 77:567 (Sept. 15) 1957. (7) Petersdorf, R. G.; Curtin, J. A., & Bennett, L. L., Jr.: Arch. Int. Med. 100:927, 1957. (8) Waisbren, B. A., & Strelitzer, C. L.: Arch. Int. Med. 101:397, 1958. (9) Holloway, W. J., & Scott, E. G.: Delaware M. J. 29:159, 1957. (10) Murphy, J. J., & Rattner, W. H.: J.A.M.A. 166:616 (Feb. 8) 1958. (11) Neter, E., & Hodes, H. L.: Pediatrics 20:362, 1957. (12) Woolington, S. S.; Adler, S. J., & Bower, A. G., in Welch, H., & Martí-Ibañez, F.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 365.



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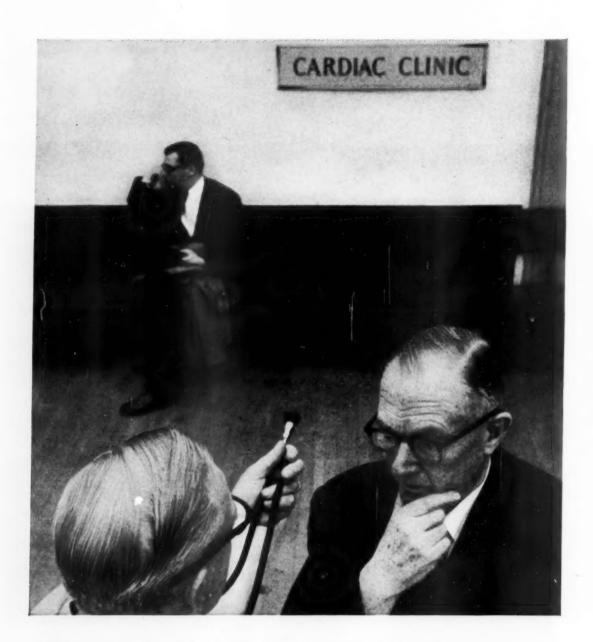
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 Shehadi, W. H.: Am. J. Gastroenterol. 28:236 (Sept.) 1957.
 Sachs, M. D.: J. Internat. Col. Surgeons 27:681 (June) 1957.

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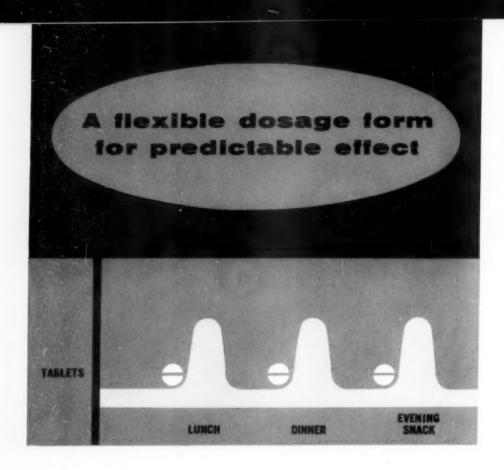
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  - 2. Freed, S.C.: G.P. 7:63 (1953)
  - 3. Sherman, R.J.: Medical Times, 82:107 (Feb. 1954)

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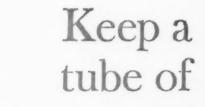
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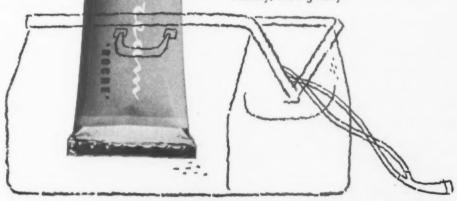
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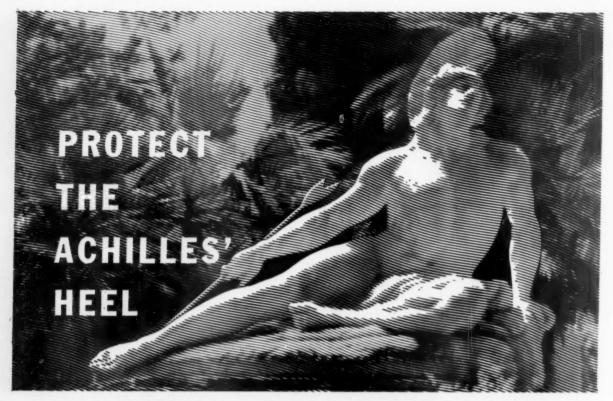
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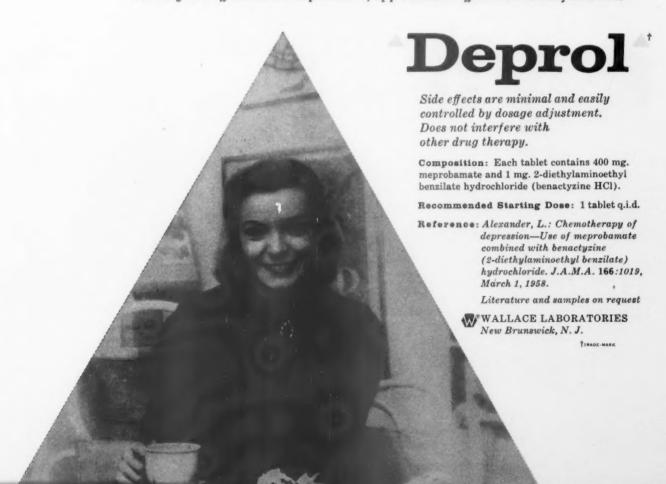


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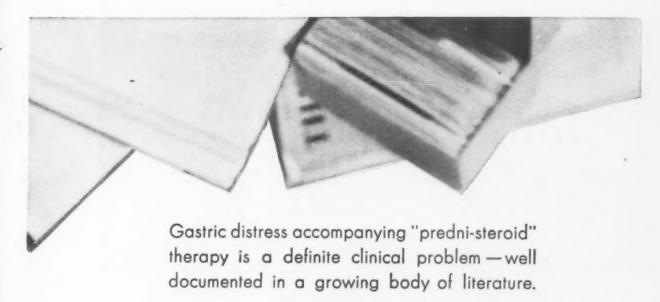


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arthritis.....



\*"In view of the beneficial responses observed when antacids and bland diets were used concomitantly with prednisone and prednisolone, we feel that these measures should be employed prophylactically to offset any gastrointestinal side effects."—Dordick, J. R. et al.: N. Y. State J. Med. 57:2049 (June 15) 1957.

\*"It is our growing conviction that all patients receiving oral steroids should take each dose after food or with adequate buffering with aluminum or magnesium hydroxide preparations."—Sigler, J. W. and Ensign, D. C.: J. Kentucky State M. A. 54:771 (Sept.) 1956.

\*The apparent high incidence of this serious [gastric] side effect in patients receiving prednisone or prednisolone suggests the advisability of routine co-administration of an aluminum hydroxide gel."—Bollet, A. J. and Bunim, J. J.: J. A. M. A. 158:459 (June 11) 1955.

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## PYELONEPHRITIS

In pyelonephritis, "the tubules suffer from damage to their lining cells which show cloudy swelling, granular degeneration and diminution in size. Inflammatory cells and colloid casts are found in the lumen of the tubules. Inflammatory cells are present also in the interstitial tissue. The glomeruli remain normal over a long period."



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Available as Tablets, Oral Suspension and Intravenous Solution.

References: 1. Smith, I. M., and Lenyo, L.: Am. Practitioner 9:78, 1958. 2. Bass, A. D.: Chemotherapy of Bacterial Infections II: Sulfonamides, in Drill, V. A., ed.: Pharmacology in Medicine, New York, McGraw-Hill Book Co., Inc., 1954. 3. Pindell, M. H., et al.: J. Pharm. Exp. Ther. 122:61A, 1958. 4. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955.

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ACHROMYCIN V dosage: Recommended basic oral dosage is 6-7 mg. per lb. body weight per day. In acute, severe infections often encountered in infants and children, the dose should be 12 mg. per lb. body weight per day. Dosage in the average adult should be 1 Gm. divided into four 250 mg. doses.

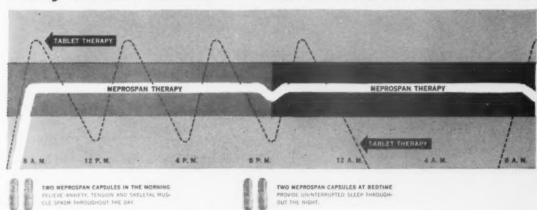
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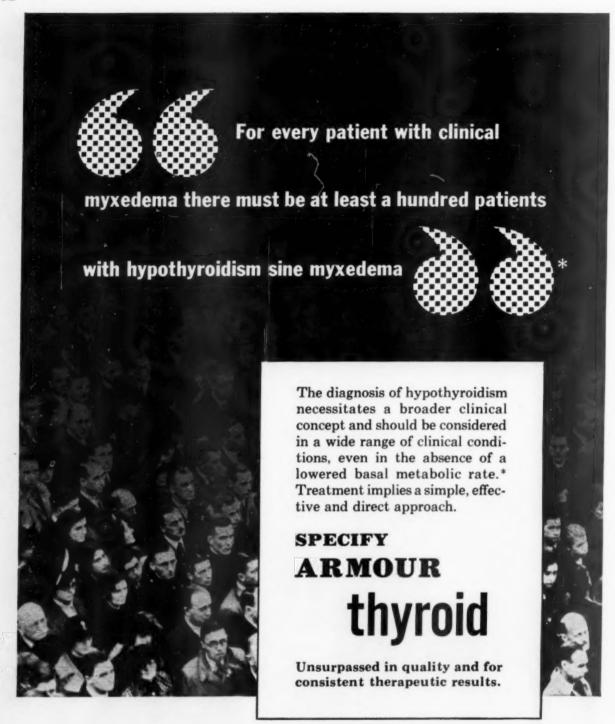
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\*Case report and photographs through the courtesy of N. Orentreich, M.D., New York, N.Y. STEROSAN®-Hydrocortisone (3% chlorquinaldol GEIGY with 1% hydrocortisone) Cream and Ointment. Tubes of 5 Gm. Prescription only.

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\*Starr, P.: Postgrad. Med. 17:73, 1955.



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1. Lewis, J.M., et al.: J. Pediat. 31:496.

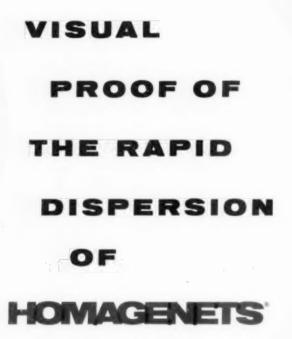
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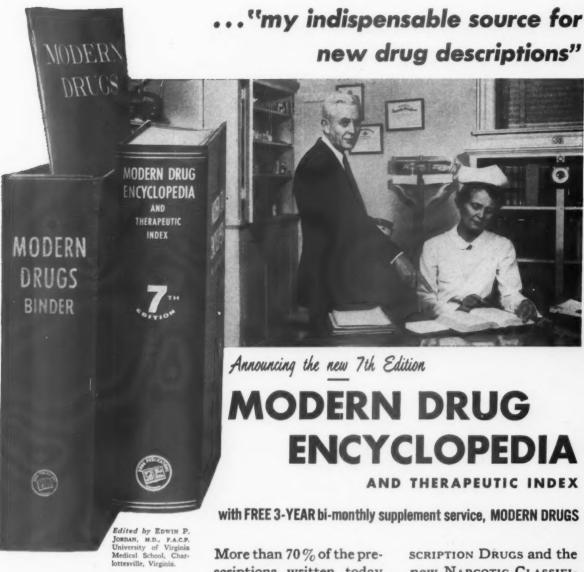
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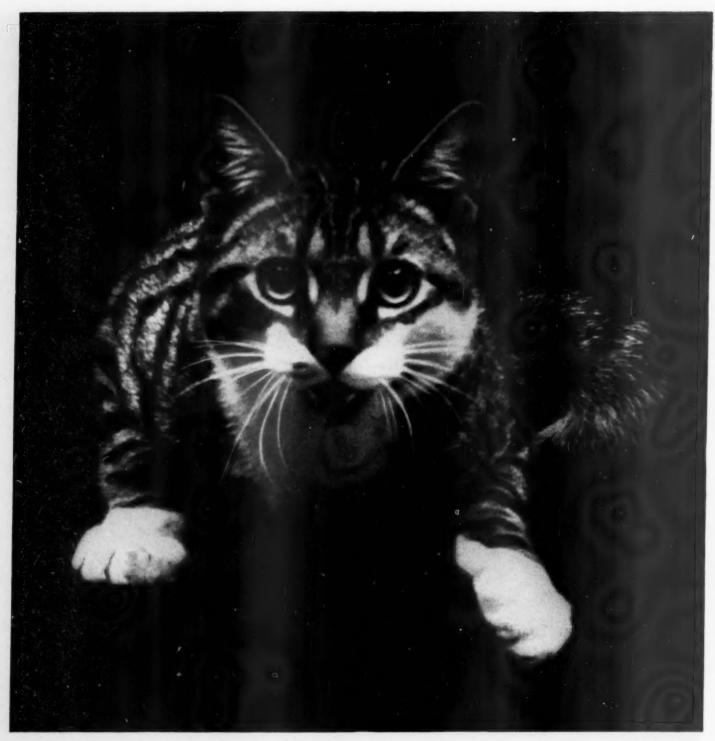


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ELIXIRS, 1 mg. and 0.2 mg. Serpasil per 4-ml. teaspoon.

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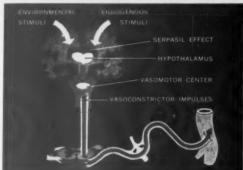
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Serpasil shields the psychic and somatic reaction centers from emotional and environmental stress stimuli, thereby inhibiting the discharge of vasoconstrictive impulses through the sympathetic nerves.

C I B A SUMMIT, N. J. 2/283584K



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References: 1. Welch, H.; Wright, W. W., and Staffa, A. W.: Antibiotic Med. & Clin. Therapy 5:52 (Jan.) 1958. 2. Carlozzi, M.: Ibid. 5:146 (Feb.) 1958. 3. Shalowitz, M.: Clin. Rev. 1:25 (April) 1958. 4. Stone, M. L.; Bamford, J., and Bradley, W.: Antibiotic Med. & Clin. Therapy 5:322 (May) 1958. 5. Cornbleet, T.; Chesrow, E., and Barsky, S.: Ibid. 5:328 (May) 1958. 6. West, R., and Clarke, D. H.: J. Clin. Invest. 17:173 (March) 1938. 7. Jimenez-Diaz, C.; Aguirre, M., and Arjona, E.: Bull. Inst. M. Res. Madrid 6:137 (Oct.-Dec.) 1953. 8. Lerman, S.; Pogell, B. M., and Lieb, W.: A.M.A. Arch. Ophth. 57:354 (March) 1957.

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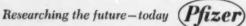
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References: 1. Council on Drugs, A.M.A.:
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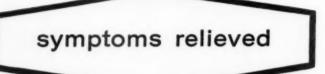
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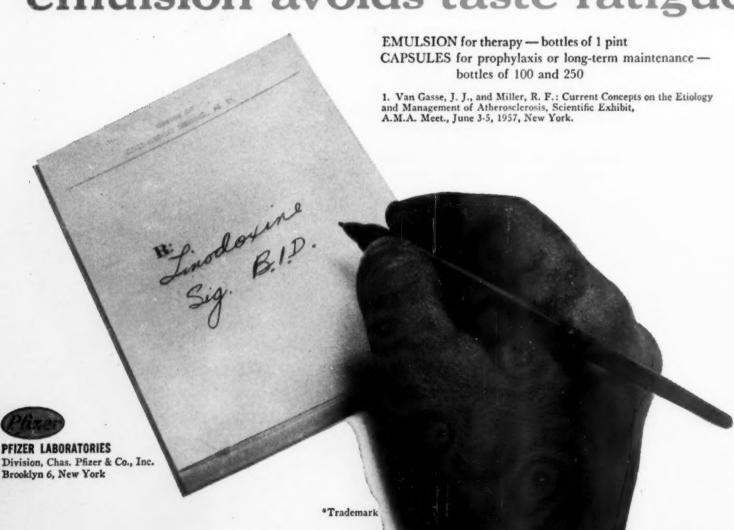




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1. Notkin, L. J.: Canad. M.A.J. 73:585 (Oct. 1) 1955.

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1. Wright, I. S.: Early use of anticoagulants in treatment of myocardial infarction, J.A.M.A. 163: 918-921, March 16, 1957.

2. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.



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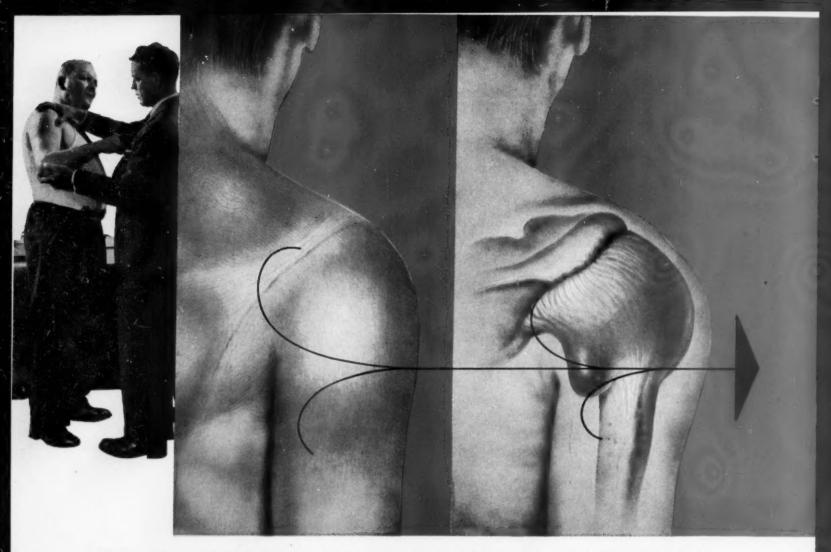
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 Comroe's Arthritis: Hollander, J. L., p. 149 (Fifth Edition, Lea & Febiger, Philadelphia, Pa. 1953).
 Merck Manual: Lyght, C. E., p. 1102 (Ninth Edition, Merck & Co., Inc., Rahway, N. J. 1956).

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References (1) Stein, 1. D.: Circulation 12:833, 1955. (2) Potvin, L.: Bull. Assoc. méd. lang. fronç. Canada 85:941, 1956. (3) Sigg, K.: Angiology 8:44, 1957. (4) Elder, H. H. A., and Armstrong, J. B.: Practitioner 178:479, 1957. (5) Braden, F. R.; Collins, C. G., and Sewell, J. W.: J. Louisiana M. Soc. 109:372, 1957.

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Holden, W. D.; Krieger, H.; Levey, S., and Abbott, W. E.: Ann. Surg. 146:563 (Oct.) 1957.

Protein hydrolysate, Mead Johnson

2. Elman, R.: J. Am. Dielet. Assoc. 32:525 (June) 1956.

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\*Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, Apr. 5, 1958. †U. S. Pat. 2,575,611



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FORD, R. V., Rochelle, J.B.III, Handley, C. A., Moyer, J. H. and Spurr, C. L.: J.A.M.A. **166**:129, Jan. 11, 1958.

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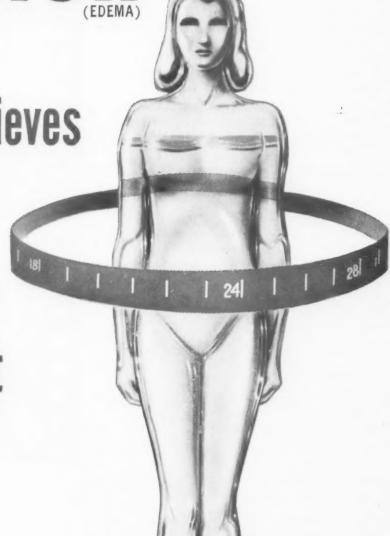
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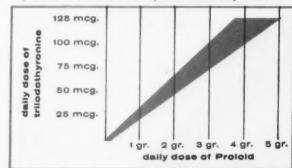
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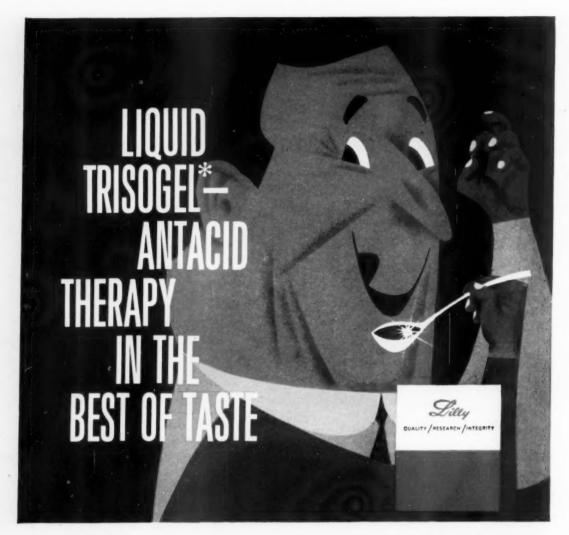
DR. NATHAN S. KLINE, Director of Research, Rockland State Hospital, Orangeburg, New York.

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## The American Journal of Medicine

Vol. XXIV

JUNE, 1958

No. 6

## Editorial

## Clinical Electrocardiography at the Crossroads

ONLY a decade ago clinical electrocardiography underwent a major reorientation when the currently employed twelve-lead system replaced the four-lead method. Today, electrocardiography again appears at the crossroads, uncertain as to its future: whether it is to follow the present course, whether it will be replaced by vectocardiography, or whether an entirely new system will evolve.

After the last war, the unipolar lead concept of electrocardiography captured the imagination of clinicians. Based on experimental studies of Wilson and his school, and supported by electrocardiographic-pathological correlations, this theory postulated that the exploring electrode connected with an indifferent electrode (Wilson's central terminal) is capable of recording from various areas of the body surface an electrical potential, the form of which resembles that taken from the surface of the heart. Thus a six-lead "semidirect" precordial lead system was developed, representing right ventricular, septal (transitional) and left ventricular leads. Furthermore, three unipolar extremity leads were added to the traditional bipolar leads, the former being thought to represent right ventricular, left ventricular and diaphragmatic wall potentials. Unipolar precordial leads could thus "explore" the chest wall, permitting recognition of anterior infarcts and abnormal right or left ventricular potentials. Additional information could be obtained from unipolar extremity leads and, if necessary, from supplementary

chest leads taken from other points on the thorax. Unusual patterns in apparently normal persons could be explained by variation in "electrical position" of the heart. To be sure, unipolar lead theory was recognized to be subject to criticism but the criticisms leveled against it seemed relatively unimportant in view of the usefulness of the theory as a whole. Enthusiasts of unipolar lead electrocardiography confidently predicted that bipolar extremity leads would soon become a thing of the past.

Simultaneously with the growth and acceptance of unipolar lead electrocardiography a few investigators began to develop vectorcardiography as a diagnostic method. Vectorcardiography, the theoretical basis of which dates back to Einthoven's time, records the same electrophysiological events as conventional electrocardiography by means of a different technic. It presents a spatial, tri-dimensional picture of the activation of the atria, and the depolarization and repolarization of the ventricles by means of loop diagrams. In order to obtain a spatial image of the electromotive forces it is necessary to find their projection in three planes: frontal, horizontal and sagittal. Electrical forces are depicted as vectors which represent their magnitude and direction in a unit of time. The depolarization of the ventricles, which inscribes the QRS complexes in the conventional electrocardiogram, can be presented vectorially in three ways: by instantaneous vectors, recorded at very short intervals, e.g., four milliseconds;

by vectors showing a larger part of the process, such as initial and terminal vectors; and finally, by vectors "summarizing" the forces, namely mean vectors. In a normal spread of the excitation wave, instantaneous vectors diverge from a zero point in a fan-like manner: a line drawn

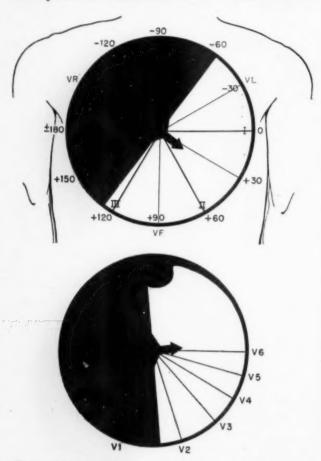


Fig. 1. Frontal plane (upper diagram) and horizontal plane (lower diagram, spine top, sternum bottom) reference systems showing the positions of the conventional electrocardiographic leads. The arrow represents the direction of the main QRS forces in an average normal individual. The clear section represents the zone of electropositivity, the black section that of electronegativity.

through the terminal points of all these vectors represents the projected QRS vector loop in a given plane. From such loops recorded in three planes a spatial loop can be obtained. A vector loop can be derived in each plane by plotting two simultaneously recorded electrocardiographic leads, which represent two axes of this plane. Loops are now most commonly recorded automatically by electrical integration of two such leads in a cathode ray oscilloscope, where the image appearing on the screen can be photographed. Thus six leads have to be recorded in three pairs, or less, if the same lead is used for

more than one plane. Vector loops can be recorded in one of the several available systems of projection of the forces onto the body surface. The cube and the equilateral tetrahedron are two systems which have been applied extensively to clinical vectorcardiography. The vector-cardiograms are analyzed by studying the spatial direction, the position and the shape of the P loops, QRS loops and T loops, and their relation to each other. Vectorcardiographic diagnostic criteria have been derived from studies of vector loops in patients with characteristic clinical and electrocardiographic features of various cardiac disorders.

Still another method of study of the electrical forces of the heart has been gaining popularity of late, namely, Grant's vectorelectrocardiography. In it the position of the electromotive forces is examined in two planes using the conventional twelve-lead electrocardiogram. Extremity leads, as has been known for a long time, reflect with reasonable accuracy the frontal plane projection of the forces. Grant pointed out that the six conventional precordial leads permit some insight into the forces' projection onto the horizontal plane [1]. Although their accuracy is relatively low, they can be placed within the horizontal plane circle as occupying a 120 degree section of its left and anterior part. (Fig. 1, lower diagram.) By estimating the direction of the forces in the two planes, it is possible to determine the approximate spatial position of the mean QRS vector, P vector and T vector. The method can also be used to determine the direction of the initial and terminal QRS forces and even permits a crude outline of the vector loops.

This application of the vector concept to conventional electrocardiography has many useful features and can be considered to be an important step in better understanding of electrocardiography. In the first place, it is consistent with current concepts of electrophysiology, which depicts the electrical activity of the heart as single dipole. By using conventional electrocardiographic leads, without additional equipment, it is easily available, and it bridges a gap between electrocardiography and vectorcardiography, providing a common meeting ground and a common language. Furthermore, it permits presentation of the abnormal electrocardiogram as a single alteration of the

<sup>1</sup> Grant, R. P. The relationship of unipolar chest leads to the electrical field of the heart. *Circulation*, 1: 878, 1950.

forces from the norm, without the necessity for memorizing various abnormal patterns in different leads.

Vectorelectrocardiography offers a theoretical basis for the various abnormalities of the clinical electrocardiogram which does not have the weaknesses of the unipolar lead theory. For example, the widely used hexaxial frontal plane reference system (Fig. 1, upper diagram), which is but a modification of Einthoven's triangle, shows that the unipolar and bipolar extremity leads are not fundamentally different from each other. but are closely related. Lead 1 in which the right arm potential is subtracted from the left arm potential (VL - VR) usually resembles lead VL closely, because it simply "views" the frontal plane forces from a point rotated 30 degrees to the right from the latter. Lead VR should not be considered a specific diagnostic lead exploring the region of the right ventricle, but it is a lead located in the negative zone of the frontal plane, the mirror image of which (-VR) falls between leads I and II and resembles one or both of these leads. It has been suggested that two extremity leads located at right angles to each other (such as I and VF; II and VL; or III and VR) contain a complete view of the frontal plane forces and therefore have to contain all the diagnostic information, which is superfluously duplicated by the remaining four leads. The five positions of the unipolar lead method in reality represent the rotation of the mean frontal plane vector to the right or left of its usual position. It appears now that it is preferable to present the position of the mean frontal plane vector as a deviation from the 0 point (the well known axis deviation of the pre-unipolar lead era) than to use the five positions. The vector concept provides a reasonable explanation for the pattern of right ventricular hypertrophy: increase in right ventricular muscle deflects the mean forces more to the right and anteriorly, thereby inscribing positive QRS complexes in leads III, VF, VR and V1 to V<sub>3</sub>. It is also preferable to apply the vector approach to the problem of myocardial infarction, rather than to think in terms of a "window" transmitting cavity potential: destruction of the electrically active fibers in the anterior wall would deflect the initial QRS forces away from the damaged area, i.e., posteriorly, thereby inscribing Q waves in precordial leads; absence of electrical activity in the diaphragmatic wall would deviate initial forces superiorly, inscribing Q waves in leads II, III and VF.

How is the clinician, who uses electrocardiography in diagnosis, affected by these different ways of presenting electromotive phenomena of the heart? Excluding arrhythmias, which are not under consideration, the clinical uses of electrocardiography fall into three broad categories: (1) the diagnosis of focal myocardial disease based on abnormalities caused by destruction of electrically active fibers, or damage to the conductive tissues; (2) alteration of the electrocardiogram caused by changes in myocardial metabolism reflecting the action of drugs, chemical agents and electrolyte disturbances; (3) recognition of the hypertrophy of one or both ventricles.

Recent advances in electrocardiographic diagnosis of focal myocardial disease have not been spectacular, although some headway is being made toward a better understanding of the relationship of some conduction defects to myocardial infarction. The widespread interest in electrolyte disturbances in recent years has resulted in more extensive use of the electrocardiogram, only to find that the relationship between such disturbances and electrocardiographic abnormalities is not reliably diagnostic, and that in individual cases the electrocardiogram may be misleading.

Considerable interest has been centered recently on the electrocardiographic recognition of enlargement and hypertrophy of the cardiac chambers. There are two apparent reasons for this: first, the availability of quantitative hemodynamic methods permits physiological-electrocardiographic correlations in various conditions to supplement pathological-electrocardiographic studies; furthermore, early recognition of ventricular hypertrophy has become a factor of considerable practical importance in certain conditions amenable to treatment. In hypertension, in acquired valvular defects and in surgically amenable congenital malformations, medical or surgical treatment is often held in abeyance until objective evidence of the harmful effects of such a lesion can be used to balance the risk of the treatment. Electrocardiographic indication of ventricular hypertrophy is often suggested as such evidence. In spite of numerous studies pertaining to electrocardiographic diagnosis of ventricular hypertrophy, the theoretical basis for such a diagnosis appears as yet to be grossly inadequate. It is not known whether electrocardiographic abnormalities observed in the presence of ventricular hypertrophy are caused

by the increase in muscular mass, by the increased size of the ventricle resulting from associated dilatation, by increased intramural tension, by some metabolic or ischemic changes vaguely referred to as "strain," or by a combination of such factors. Yet there seems to be a growing tendency to represent electrocardiography as an exact, quantitative method for the diagnosis of various anatomical relationships. In recent writings, especially pediatric and surgical, the impression may be gained that the electrocardiogram is capable of estimating the height of the right ventricular pressure or the magnitude of pulmonary blood flow; of differentiating between atrial and ventricular septal defects, or even between high and low atrial septal defects. While this is based on correlations between physiological and anatomic findings and the electrocardiogram, such a relationship can apply only to a group of cases and is not likely to be accurate in any individual case. Recent studies in our laboratory [2,3] have shown that the electrocardiographic pattern of left ventricular hypertrophy is reasonably accurate when tested against pathologic evidence of such hypertrophy, but an appreciable number of false-negative and false-positive cases were found. This illustrates the point that a relationship demonstrated reliably for a group of cases often fails in an individual case.

It is disturbing to see strictly hemodynamic terms such as "systolic overload" and "diastolic overload" find their way into the electrocardiographic vocabulary. No evidence has ever been presented that hemodynamic events are in any way reflected in the electrocardiogram. It is particularly noteworthy that the most significant hemodynamic event in clinical medicine, the change from a compensated state to cardiac failure and vice versa, occurs without any known electrocardiographic alterations.

A clinician who uses electrocardiography as an aid in diagnosis should be fully aware of the limitations of this procedure. Electrocardiographic patterns inform us that the electrical potential recorded from various parts of the

body surface differs from the norm. Such a finding depends not only on an abnormal spread of the forces through the heart but also on the conduction of such forces to the surface of the body. Therefore, the anatomical position of the heart in the thorax, the conductivity of the intermediate structures, and the distance of the electrode to the heart may influence the type of surface potential recorded in conventional leads. An electrocardiographic abnormality merely suggests a certain anatomical condition within the heart with a variable degree of probability, which can never reach a 100 per cent level. It is also necessary to apply caution in expressing the limits of normal of the various measurements, such as voltages, duration of ORS complexes, width and duration of Q waves and others, because of the indirect nature of conventional curves whereby forces are estimated from measurements at distant points.

The clinician may ask whether vectorcardiography and vectorelectrocardiography have increased or are likely in the future to increase materially the diagnostic accuracy of the electrocardiogram. Thus far, this has not been demonstrated. The immediate future of vectorcardiography is not clear. Expensive equipment notwithstanding, it is now in a state of confusion because of the unavailability of an entirely satisfactory system. There seems to be a feeling that neither of the two systems now in clinical use will ultimately be found acceptable [4]. If a new system is designed, all present diagnostic criteria may have to be revised because vector loops recorded with different technics may show important differences. Furthermore, there are inherent weaknesses in the vector method, such as the absence of information regarding rhythm and rate, difficulty in timing and measuring various complexes, and lack of detail of P waves, S-T segments and T waves. Finally, vector loops, being an integration of two scalar electrocardiographic leads, cannot contain more information than the two leads from which they are derived.

It is difficult to project present trends into the future. Perhaps an ideal vector system will be found which could also be used interchangeably with scalar leads. Perhaps only a half-dozen key electrocardiographic leads will be agreed upon. Perhaps, with modern electronic equipment, high fidelity tracings will be obtained which will

<sup>4</sup> HECHT, H. H. Editor. The electrophysiology of the heart. Ann. New York Acad. Sc., 65: 653-1146, 1957.

<sup>&</sup>lt;sup>2</sup> Selzer, A., Ebnother, C. L., Packard, P., Stone, A. O. and Quinn, J. E. Reliability of the electrocardiographic diagnosis of left ventricular hypertrophy. *Circulation*, 17: 225, 1958.

<sup>&</sup>lt;sup>3</sup> Selzer, A., Naruse, D., York, E. and Pierce, C. The reliability of the electrocardiographic diagnosis of left ventricular hypertrophy. п. The absence of LVH pattern in hypertrophied hearts. Clin. Research, 6: 49, 1958.

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permit outlining the spread of excitation in much more detail than is now possible. A clinician cannot help wondering whether or not such advances will be of such practical value. Suppose a refined picture of the electromotive forces would permit a detailed outline, a "map," of a myocardial infarct, will this be important to the clinician? Suppose that a small silent area will be found which by present methods is not detectable, will we be able to distinguish a small section of dead muscle from an unusual distribution of the Purkinje system?

Electrocardiography is, and is likely to remain, a purely empirical diagnostic method. Its clinical application stems not from electrophysiological theories but from correlation with various structural abnormalities of the heart. Because of this empirical nature, it would seem irrelevant whether electrocardiographic tracings

are interpreted with the aid of the spatial vector approach, or with the aid of the partly discredited unipolar-lead theory, or with no system at all but simply by memorizing a sequence of waves and deflections which occur under abnormal conditions. Electrocardiography is a method of recording the electrical potential variation of the heart muscle, which has no known specific relationship to cardiac disease. As a diagnostic method it is therefore indirect, once removed from clinical medicine. It is a very important part of the armamentarium of the clinician dealing with cardiac disease, yet a clinical diagnosis cannot stand or fall on electrocardiographic evidence alone.

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## Tricuspid Stenosis\*

### Clinical Features in Twelve Cases

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THE diagnosis of tricuspid stenosis has been a challenge to clinicians since the discovery that physical signs could be used to identify valvular lesions of the heart. Corvisart [7] first recognized that stenosis of either atrioventricular valve could produce a precordial thrill, but remarked that the signs of tricuspid stenosis were surrounded by obscurity. Corvisart's most famous pupil, Laennec, did not mention tricuspid valvular murmurs in his treatise on mediate auscultation [2]. Bertin in 1824 described a diastolic murmur in tricuspid stenosis like the " . . . sound of a blow given by a file on wood or that of a bellows quickly pressed . . . heard at the inferior portion of the sternum" [3] and apparently was able to make the diagnosis successfully during life. Hope also was aware of the murmur of tricuspid stenosis, but admitted that he had not heard one [4].

Almost a hundred years ago Duroziez presented in detail ten cases proved at autopsy [5]. In all but one associated mitral and aortic valvular disease was present. He stressed the importance of a diastolic murmur (occasionally like the "roulement" of mitral stenosis) at the inferior portion of the sternum as a clinical sign. It is of significance that although one of his patients with stenosis and insufficiency of the mitral and tricuspid valves and aortic insufficiency was able to lie remarkably flat almost to the end, respiratory symptoms were prominent in the others including a patient with isolated tricuspid stenosis. Herrick, on the other hand, emphasized the respiratory comfort of the patient with tricuspid stenosis in the presence

of edema and cyanosis [6]. Shattuck stressed the association of tricuspid obstruction and edema [7].

Despite the teachings of these early observers, until recently the diagnosis of tricuspid obstruction has been made infrequently during the lifetime of the patient. Indeed, Cabot in discussing a case correctly assessed only at necropsy, was forced to state in 1930: "I do not know how to diagnose tricuspid involvement. . . . If people put that down in their diagnosis before autopsy they are generally wrong" [5]. Although tricuspid diastolic murmurs were identified occasionally and separated from murmurs produced by the mitral valve, more diagnostic importance came to be attached to a history of anasarca, especially ascites, with slight dyspnea, prominent venous pulsations, associated mitral and aortic involvement, and the combination of icterus and cyanosis (icterocyanosis) [7].

The technic of cardiac catheterization affords the opportunity to confirm the diagnosis of tricuspid stenosis in the living patient, and thus facilitates a more adequate appraisal of the clinical manifestations of this lesion and recognition of those signs and symptoms that are most helpful in diagnosis. Evaluation of tricuspid valvular function has become an integral part of the clinical evaluation of patients with valvular heart disease, especially those being considered for surgical intervention. Several recent reports have described patients with tricuspid stenosis in whom the diagnosis was made during life [9-14], but no extensive analysis of the range of clinical manifestations

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TABLE I CLINICAL DATA IN TWELVE PATIENTS WITH TRICUSPID STENOSIS

Dariana	Age	Pro	Pulmonar	Symptoms	E4	Ascites	Abnormal	Tri	cation icuspid urmur	Tricuspid	Tricuspie
Patient	(yr.), Sex	Diagnosis	Dyspnea	Orthop- nea	Edema	Ascites	Jugular Pulsation	Inter- costal Space	Cm. Left of Sternum	Murmurs	Thrill
F. C.*	35, F	NSR: TS	++	0	++	0	0	4	3	D, P	P
E. R.	49, F	NSR; MS, TS	++	0	0	0		3	4	P	P
J. P.†	30, F	NSR; MS, TS	++,	0	0	0	P P	3	5.5	D, P	P
R. P.	42, F	NSR: MS, TS	++	+	+	0	Р	4	4	P	P
	46	AF; MS, MI, AS, AI, TS, TI	+	+	++	0				D, S	D, S
E. H.	23, F	NSR; MS, AS, AI, TS	++1	0	+1	0	P	5	4	P	P
R. G. 1	24, M	NSR; MS, MI, AI, TS, TI	+++	+++	+++	0	0	4	4.5	D, P, S	D, S
S. G.¶	37, F	AF; MS, MI, TS, TI	++	+++	+++	+	S	4	3	D, S	D
R. R.	41, F	AF; MS, MI, AS, AI, TS, TI	+++	+++	+++	+++	S	5	6	D, S	D
A. N.	31, F	AF; MS, MI, AS, AI, TS, TI	+++	+++	+++	+++	S	5	6	D, S	D D D
L. R.	52, F	AF; MS, MI, TS, TI	+	++	++	++	S	5	6	D, S	D
J. F. §	33, F	AF; MS, MI, AS, AI, TS, TI	+++	++	++	+	S	5	3	S	0
G. P.**	39, F	AF; MS, MI, AS, TS, TI	+++	+++	+++	+	S	5	6	D, S	D

Note: NSR = Normal sinus rhythm

AF = Atrial fibrillation

MS = Mitral stenosis MI = Mitral insufficiency

AS = Aortic stenosis

AI = Aortic insufficiency

TS = Tricuspid stenosis
TI = Tricuspid insufficiency

O = Absent

+ = Moderate

+ = Severe S = Systolic

D = Early or mid-diastolic

Intermittent, mild

P = Presystolic

\* Tricuspid valvuloplasty. † Mitral valvuloplasty.

During pregnancy only.

Died, autopsy.

Mitral and tricuspid valvuloplasty.

in patients with this lesion has yet appeared.

We are reporting our experience with twelve patients with tricuspid stenosis. The hemodynamic criteria for diagnosis and the physiologic abnormalities in ten of these patients have been reported previously [15]. Five cases are presented in detail to emphasize the variable manifestations of the lesion. The clinical data of the twelve patients are discussed in relation to the hemodynamic data, and with particular reference to the symptoms and signs which have been considered of aid in the diagnosis. The hemodynamic data of patients G. P., R. G. and from the second study of patient R. P. are presented since they have not been reported previously.

#### MATERIALS AND METHODS

The diagnosis of tricuspid stenosis was made clinically in eleven of the twelve patients on the basis of a characteristic murmur and thrill, and was confirmed by cardiac catheterization. In one patient, it was suspected on review or the catheterization data and confirmed at postmortem examination. Eleven patients had rheumatic heart disease with multivalvular involve-

ment; one had isolated tricuspid stenosis of uncertain etiology. Each patient was examined personally by us. All pertinent electrocardiograms, chest roentgenograms and laboratory data have been reviewed. Angiocardiograms were performed and interpreted by Dr. Israel Steinberg in six patients. Four patients underwent mitral valvuloplasty; one of these also had a tricuspid valvuloplasty. One patient had only a tricuspid valvuloplasty. Another patient died while being prepared for surgery and autopsy was obtained. The diagnosis therefore was confirmed anatomically in four patientsby surgery in two patients and at autopsy in another two.

#### CLINICAL DATA

All but one of the patients were women. Five had a history of polyarthritis or chorea in childhood. In nine, murmurs had been detected prior to age sixteen. The age of the patients ranged from twenty-three to fifty-two years. (Table 1.)

Symptoms: Symptoms were variable. Every patient at one time or other had suffered from dyspnea on exertion. (Table 1.) Severe exertional dyspnea, accentuated during pregnancy,

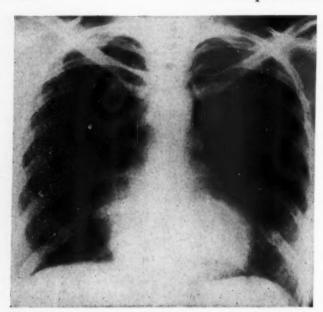


Fig. 1. Chest roentgenogram of patient F. C. with isolated tricuspid stenosis. Note enlarged right atrium with normal right ventricle, pulmonary arteries, left atrium and ventricle (confirmed by angiocardiogram).

was the major symptom in patient J. P. and was relieved following a mitral valvuloplasty. Respiratory complaints in S. G. also improved following mitral and tricuspid valvuloplasty. Orthopnea was pronounced in the eight patients with chronic fluid retention. Dyspnea and orthopnea were worse when edema was most pronounced and were relieved incompletely by diuresis. In no instance could it be established that pulmonary symptoms improved after the development of right heart failure or tricuspid insufficiency.

Chronic edema, requiring mercurial diuretic therapy, occurred in every patient with atrial fibrillation, and in one patient (R. G.) with normal sinus rhythm; all patients in this group had associated tricuspid insufficiency and mean right atrial pressures at rest of 12 mm. Hg or greater. In the four patients with normal sinus rhythm who did not have tricuspid insufficiency, edema was intermittent in two and absent in two. Mean right atrial pressures in this group were 8 mm. Hg or less. Signs of intraperitoneal fluid were noted in six patients but persistent ascites was a major problem in only three, all of whom had multivalvular lesions and atrial fibrillation.

Severe fatigue was a complaint in ten patients and was a prominent symptom in five. Although E. H. had noted edema and shortness of breath on exertion during her two pregnancies, she had never suffered from undue fatigue. She is the only patient in the series who had a normal cardiac output during both rest and exercise. In nine of the twelve patients a triad of symptoms, fatigue, dyspnea and edema, was present.

Physical signs: Evidence of pulmonary edema was present in seven patients, all of whom were first seen in severe right heart failure with associated pulmonary symptoms. Hepatomegaly was encountered in all but three. Two of those with a history of edema did not have enlargement of the liver. The largest livers were observed in patients with atrial fibrillation and tricuspid insufficiency as well as stenosis. In the six patients with normal sinus rhythm, distinct presystolic pulsations of the liver were present in three, one of whom did not have a history of edema. Prominent presystolic pulsations of the external jugular veins were observed in four. Patient F. C. with isolated tricuspid stenosis had no unusual pulsations in the neck veins. Systolic pulsations of the liver and external jugular veins were present in all six patients with atrial fibrillation and tricuspid insufficiency. Although dusky nailbeds and extremities were often observed, especially during severe heart failure, the peculiar combination of jaundice and cyanosis (icterocyanosis) described by Wearn [16] was not noted.

The degree of cardiac enlargement and the character of the apical impulse were dependent mainly on the associated valvular lesions. In the patient with pure tricuspid stenosis (Fig. 1) there was no enlargement of the heart on physical examination. Marked enlargement to the right of the sternum was readily appreciated in patients S. G. and L. R.

A tricuspid diastolic thrill and murmur were detected in eleven instances. (Table 1.) Both were present usually in the third, fourth or fifth intercostal space between the left sternal border and the nipple line. (Fig. 2.) The fifth intercostal space parasternally was the most frequent site of maximal intensity. The murmur was early and mid-diastolic when associated with atrial fibrillation, and diastolic-presystolic with normal sinus rhythm. In R. P. the murmur and thrill changed from presystolic to early and middiastolic with the onset of atrial fibrillation. The murmur was low in pitch, coarse and rumbling in character but gave the impression of being higher pitched and closer to the ear than the associated murmur of mitral stenosis. It was heard better with the bell stethoscope attachment than with the diaphragm. The thrill was

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of higher frequency than the thrill of the accompanying mitral stenosis; occasionally it was localized to a fingertip area. In every case the thrill became coarse and stronger with inspiration. "Step-wise" auscultation from the apex to the tricuspid area was helpful in separating the tricuspid diastolic murmur from the mitral diastolic murmur. The mitral murmur decreased in intensity medially and a small relatively silent area could usually be found between the two valve areas. Although the murmur of tricuspid insufficiency occasionally radiated far enough laterally toward the apex to be confused with that of mitral insufficiency, the murmur of tricuspid stenosis was more localized. However, on occasion it radiated to the pulmonic area and in one instance to the aortic area. Several patients had a high-pitched, diminuendo diastolic murmur of aortic or pulmonic insufficiency, which was readily separated from that of tricuspid stenosis. Localized in the same area as the tricuspid diastolic murmur, a sharp clicking sound which followed the second sound was heard in three patients and was interpreted as an opening snap of the tricuspid valve.

In every instance the murmur of tricuspid stenosis and, if present, that of associated tricuspid insufficiency increased in intensity during inspiration and decreased during expiration. The increase in intensity was usually dramatic and sustained throughout inspiration, but in a few instances the accentuation occurred only during a few cardiac beats early in inspiration. Conversely the murmurs at the mitral area faded during inspiration and became more intense during expiration. The auscultatory and palpatory changes with respiration provided the most convincing clinical evidence that the murmurs at the tricuspid area did not originate from the same source as those at the apex.

Roentgenograms: Enlargement of the right atrium was encountered in every patient. (Figs. 1, 2 and 3) and was noted best in the frontal and right oblique views. In three patients (S. G., A. N., and L. R.) the atria were gigantic and displaced the right border far into the lung. (Fig. 3.) In another three patients (E. R., E. H., and R. P.) the atria were only mildly to moderately enlarged. The largest right atria were encountered in the patients who had both tricuspid stenosis and insufficiency, atrial fibrillation and right atrial pressures of 12 mm. Hg or greater at rest. When a giant left atrium was combined with a giant right atrium the cardiac

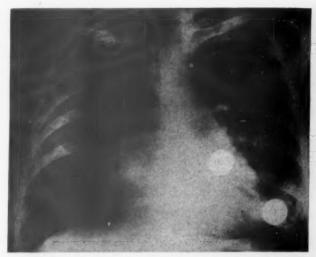


Fig. 2. Chest roentgenogram of patient J. P. with tricuspid and mitral stenoses. Right atrium is moderately enlarged. Outline of large left atrium is seen within cardiac shadow. Lower, lateral, white spot is shadow of coin attached to patient at site of mitral diastolic murmur and thrill; upper, medial spot marks site of tricuspid murmur and thrill.

silhouette was massive. (Fig. 3.) The angiocardiogram was characteristic. (Fig. 4.) The right atrium was enlarged and its opacification was prolonged. In the frontal films the tricuspid valve could be localized precisely as a thin line separating the well-opacified right atrium from the less dense right ventricle. Abnormalities of the right ventricle, pulmonary artery and left heart reflected the associated valvular lesions.

Electrocardiograms: Six patients were in normal sinus rhythm at the time of study. In two patients with atrial fibrillation electrocardiograms taken twelve and five years earlier and showing sinus rhythm were available. Sharply peaked P waves of increased amplitude consistent with right atrial enlargement were present in all eight tracings. (Figs. 5 and 6.) The configuration was most striking in leads II, V1 and V2, in which the amplitude of P ranged from 0.25 to 0.4 millivolts. In two patients (F. C. and E. R.), neither of whom had right ventricular hypertrophy or hypertension, the amplitude of the P wave in  $V_1$  was greater than that of the QRS complex. (Fig. 6.) Bifid P waves of increased duration were present in five of the seven patients with combined mitral and tricuspid stenosis. Six patients, including one with isolated tricuspid stenosis, had P waves greater than 0.11 seconds in duration, evidence for intra-atrial block [17]. Seven had small rsr' ventricular complexes in the right precordial leads. One patient, R. P., had complete right bundle

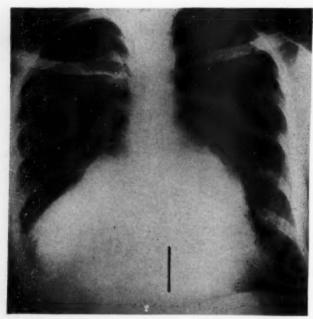


Fig. 3. Chest roentgenogram of patient L. R. with stenosis and insufficiency of tricuspid and mitral valves. Right atrium is of giant size; left atrial appendage bulges prominently along left border of heart. Line drawn within cardiac silhouette indicates location of tricuspid valve as defined by angiocardiogram.

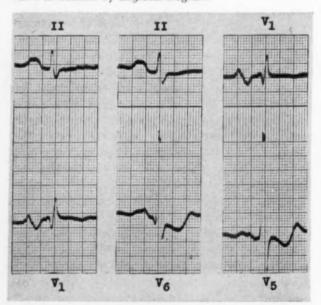


Fig. 5. Simultaneously recorded, overstandardized electrocardiographic leads in patient R. G. with stenosis and insufficiency of tricuspid and mitral valves, aortic insufficiency and enlargement of right and left atria. Record speed: 50 mm./second. P waves are diagnostic of combined atrial hypertrophy. They are broad and bifid in leads  $\pi$ ,  $V_{\delta}$ ,  $V_{\delta}$ ; peaked and diphasic in  $V_{1}$ . Peak of P in  $V_{1}$  coincides with first peak of bifid P in other leads.

branch block with an rsR' pattern in V<sub>1</sub>. A qR pattern in V<sub>1</sub> suggestive of right atrial hypertrophy was present only in A. N. The amplitude

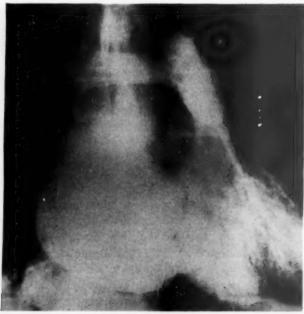


Fig. 4. Angiocardiogram of patient E. R. with tricuspid and mitral stenoses. Right atrium is moderately enlarged and densely opacified. Tricuspid valve is displaced to left and appears as a narrow unopacified curvilinear band between right atrium and ventricle. Opacification of atrium was prolonged.

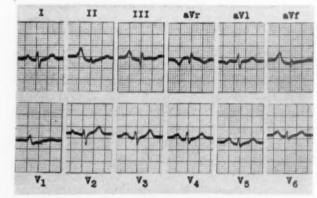


Fig. 6. Electrocardiogram of patient F. C. with isolated tricuspid stenosis. Standardization: 1 mV./cm. Amplitude of QRS complexes is low. Small rsr' in  $V_1$ . P waves are of increased duration and amplitude and taller than QRS in  $\pi$ , aVf,  $V_1$ .

of the QRS complexes was unusually low in four instances and in three was combined with tall P waves of greater amplitude than the QRS in some leads.

Laboratory data: Polycythemia was not present in any patient. Liver function studies were often slightly abnormal; persistent increase in serum bilirubin was not encountered. Variable degrees of proteinuria were present in only four patients. The blood urea nitrogen was intermittently elevated in this same group.

#### PATHOLOGIC FEATURES

Two patients (R. G. and J. F.), came to autopsy. Both had tricuspid stenosis as well as insufficiency and mitral and aortic valvular disease. The tricuspid leaflets were fused to form a shallow funnel with an oval orifice projecting into the right ventricle. (Fig. 7.) The line of commissural fusion was barely discernible. The cusps were only slightly thickened and the chordae were not extensively involved. The tricuspid valves were less deformed than the mitral valves, which were markedly thickened, calcified, severely stenotic (Fig. 7) and displayed extensive chordal deformity. In patient S. G., who underwent both mitral and tricuspid valvuloplasties, the tricuspid valve was also less stenotic than the mitral as judged by digital palpation during the operations.

#### CASE REPORTS

Case I. F. C., a thirty-four year old white telephone operator, was admitted to the New York Hospital on January 25, 1955, complaining of fatigue and edema. A murmur attributed to mitral stenosis had first been detected at age fourteen. For ten years she had been aware of tiring easily. Intermittent swelling of the abdomen and ankles had been present for two years. During the year prior to admission, edema of the face, hands and legs, and abdominal fullness had appeared following a picnic. At that time blood pressure and serum proteins were normal; serum non-protein nitrogen was 36 mg. per cent and the urine contained four-plus protein, occasional white blood cells and red cells. She had never noted hemoptysis, cough, nocturnal dyspnea or wheezing.

On admission she was able to lie flat without discomfort. The blood pressure was 130/90 mm. Hg. The neck veins were not distended and there were no unusual pulsations. The liver was not palpable. There was slight pretibial edema. In the fourth left intercostal space, 3 cm. from the left sternal border, was a grade 3\* mid-diastolic rumble with presystolic accentuation accompanied by a purring thrill. The first sound in the tricuspid area was loud and snapping. The intensity of both murmur and thrill increased with inspiration. No other murmurs were apparent.

Roentgenograms (Fig. 1) and fluoroscopy of the chest, and angiocardiograms demonstrated an enlarged right atrium. The ventricles, left atrium and pulmonary artery were normal. There was no albuminuria. The hemogram was normal. Blood urea nitrogen was 10 mg. per cent, the urea clearance was 66 per cent of normal. The electrocardiogram is illustrated in Figure 6. Cardiac catheterization con-

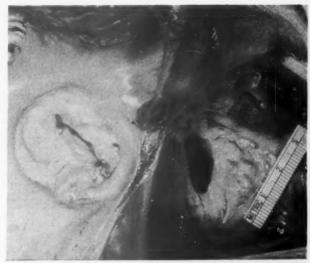


Fig. 7. Tricuspid (right) and mitral valves of patient R. G. viewed from above. Mitral valve is severely stenotic, thickened and calcified with slit-like orifice. Tricuspid valve is less stenotic, also insufficient, less thickened and not calcified. Commissures are not identified. Planimetry of tricuspid orifice in this photograph yielded an area of 1.1 sq. cm., identical with area estimated from catheterization data.

firmed the clinical diagnosis of isolated tricuspid stenosis. There was a diastolic pressure gradient of 4.7 mm. Hg at rest and 11.7 mm. Hg during exercise across the tricuspid valve. The cardiac output was strikingly reduced at rest and during exercise. Pressures in the right ventricle, pulmonary artery and pulmonary "capillary" position were normal at rest and during exercise.

At tricuspid valvuloplasty, performed by Dr. Laurence Miscall, the right atrium and atrial appendage were greatly enlarged; the pulmonary artery and both ventricles appeared normal. A presystolic thrill was felt over the right atrium. The tricuspid valve was estimated as "not more than 1 sq. cm." in area. A biopsy specimen of the right atrial appendage did not demonstrate Aschoff's bodies. Following surgery, dyspnea, palpitations and fatigue were less prominent. Cardiac catheterization performed fourteen months after valvuloplasty revealed persistence of a significant gradient across the tricuspid valve, a greater increase in output during exercise, slight elevation of the pulmonary "capillary" pressure and, as previously, normal right ventricular and pulmonary artery pressures.

Comment: Although previously attributed to mitral stenosis, the characteristic murmur and thrill over the tricuspid area established a diagnosis of tricuspid stenosis. Involvement of other valves could not be demonstrated by physical examination, cardiac catheterization, angiocardiogram or at operation.

<sup>\*</sup> Based on four grades.

Fatigue and mild intermittent edema were the predominant symptoms. Pronounced edema occurred transiently after a period of increased physical activity and unrestricted salt ingestion. It is doubtful that the hemodynamic alterations at rest were alone sufficient to cause salt and water retention.

Isolated tricuspid stenosis is very rare. Review of the literature reveals only four other cases. Duroziez [5] described the case of a sixty-four year old concierge whose valve, "most probably insufficient as well as stenotic," would admit only one finger. A systolic murmur ("jet de vapeur") had been heard over the sternum. The patient had marked edema, and prior to death was forced to rest constantly in a armchair because of severe orthopnea. Gibson and Wood [13] described a thirty-three year old man with isolated tricuspid stenosis, which was confirmed by catheterization. Lupus erythematosus was thought to be the cause of the valvular lesion. An infant studied by Lewis [18] had congenital tricuspid stenosis and died shortly after birth. Gordon and co-authors [19] recently presented a case of isolated rheumatic stenosis which was confirmed at operation. A presystolic murmur was heard to the right of the xiphoid cartilage as well as at the apex. In other reports of congenital or acquired tricuspid stenosis the lesion was complicated by additional cardiac anomalies or valvular defects.

The etiology of the lesion in the present instance must remain in doubt. There is no evidence of a systemic disease process secondarily affecting the heart. Tricuspid stenosis is a frequent occurrence in the endomyocardial fibroelastosis of the Bantu [20], but to our knowledge has not been found as an isolated entity in the form of endocardial fibroelastosis which is encountered in Europe and North America [21]. A congenital etiology cannot be excluded entirely, but rheumatic fever is the most likely cause.

CASE II. E. R., a forty-nine year old white woman, was admitted to the New York Hospital on April 17, 1955, for evaluation of her cardiac disease. She had had active rheumatic fever at age eight, following which a heart murmur was detected. For three years prior to admission she had been subject to severe fatigue and moderate dyspnea during heavy housework but she had not required cardiac medication and had never noted edema. On admission she was able to climb one flight of stairs slowly before fatigue caused her to stop, and could walk six blocks on the

level. She was able to sleep in a flat position without discomfort.

Physical examination revealed normal sinus rhythm at a rate of 80 and a blood pressure of 118/78 mm. Hg. The external jugular veins were distended with the patient in a supine position and pulsated in presystole. The liver was two fingerbreadths below the right costal margin and pulsated in presystole. The heart was not enlarged. The first sound was accentuated at the tricuspid area but not at the apex. At the apex a presystolic murmur and thrill of mitral stenosis were observed. In the third intercostal space 4 cm. to the left of the sternum a separate presystolic murmur and thrill were present and were followed by a third sound, interpreted as an opening snap arising from the tricuspid valve. With inspiration the intensity of the tricuspid murmur and thrill increased whereas the mitral murmur decreased in intensity.

Urinalysis, blood count and serum proteins were normal. In the electrocardiogram the P waves were peaked with an amplitude of 0.15 mV in V<sub>1</sub> and 0.3 mV in V<sub>2</sub>. QRS in V<sub>1</sub> was less than 0.1 mV in amplitude. An angiocardiogram demonstrated moderate enlargement of the right atrium, right ventricle and left atrium. (Fig. 4.) There was a clear line of demarcation between the atrium and ventricle in the plane of the tricuspid valve, and opacification of the atrium appeared unusually prolonged.

Comment: Despite the slight hepatomegaly and the absence of edema and venous engorgement a diagnosis of tricuspid stenosis was made after the detection of a diastolic murmur and thrill in the tricuspid area. These were differentiated from the murmur and thrill of the associated mitral stenosis by observing their changes during respiration. The tall, peaked P waves and the low voltage of QRS<sub>V1</sub> in the electrocardiogram provided additional, but non-specific, clues. Cardiac catheterization revealed a gradient from right atrium to right ventricle during right ventricular diastole of 6.5 mm. Hg at rest and 14 mm. Hg during exercise, thus confirming the diagnosis [15]. The mitral valve orifice area was estimated to be 1.0 sq. cm. and the tricuspid 0.7 sq. cm.

The absence of edema was probably related to the resting right atrial mean pressure of only 8 mm. Hg, which is less than the level commonly associated with renal salt and water retention [22]. Although the pressure rose to 17 mm. Hg during exercise, voluntary restriction of activity limited the periods of venous hypertension. The patient's outstanding symptom was severe fatigue which was correlated with the striking reduction of resting cardiac output to 1.52 L./minute/M² and the deficient rise to 1.90 L./

TABLE II HEMODYNAMIC DATA IN THREE PATIENTS WITH TRICUSPID STENOSIS

		Oxygen Con-	Cardiac				Pressures	(mm. Hg)			Pul- monary		ves Area cm.²)
Patient	State	sumption (ml./ min./ M³ B.S.A.)	Output (L./ min./ M² B.S.A.)	Rate	Pul- monary "Capil- lary" Mean	Pul- monary Artery Systolic/ Diastolic, Mean	Right Ventricle End Diastolic	Right Atrium Mean	Brachial Artery Systolic/ Diastolic, Mean	Mean Tricuspid Gradient	Vascular Resist- ance (dynes- sec cm5)	Mitral	Tricuspid
R. P.	Rest	103	2.48	68	11	24/9, 14	0	5		2.9	57	1.2	1.2
	Exercise	231	2.53	88	24	35/20, 28	2	7		5.6	74	1.0	1.2
R. P.*	Rest	110	1.91	64	15	30/15, 19	10	11	119/72, 87	4.3	98	0.9	0.9
	Exercise	218	2.09	84	25	45/25, 32	11	16		7.4	160	0.8	0.8
R. G.	Rest	164	2.13	92	33	50/33, 39	2	12	108/68, 80	10.7	131	0.7	1.1†
	Exercise	213	2.01	128	46	61/44, 51	8	22		15.6	115	0.5	0.6
G. P.	Rest	124	1.06	64	25	82/31, 44	12	17	104/69, 80	5.3	986	0.4	0.5

\* Second study, forty months later

† Corrected for tricuspid regurgitation.

minute/M<sup>2</sup> during exercise. The cardiac output, pulmonary vascular pressures and pulmonary vascular resistance were lower than expected for her degree of mitral stenosis [15]. By limiting venous inflow the tricuspid stenosis could be interpreted as "protecting" the pulmonary bed from the devolutionary changes generally associated with "tight" mitral stenosis.

CASE III. R. P., a forty-seven year old white housewife, was admitted to the New York Hospital in April, 1957, for her second cardiac catheterization. She had had chorea at ages nine and twelve, and rheumatic fever with arthritis at age seventeen. Her first pregnancy at the age of twenty-two was complicated by edema of the face and legs, and her second, six years later, was terminated by therapeutic abortion in the fourth month because of progressive shortness of breath and edema. She had suffered from exertional dyspnea since the age of thirty-one. Intermittent edema appeared at age thirty-six. Persistent edema and fatigability had been present for eight years.

During her first admission in December, 1953, the pulse was regular and the blood pressure was 129/88 mm. Hg. The lungs were clear. A presystolic murmur and thrill ending in an accentuated first sound were present at the apex. A separate presystolic murmur and thrill were noted in the tricuspid area. The liver was slightly enlarged. There was moderate pretibial edema. Routine urinalysis and complete blood counts were normal. The blood urea nitrogen was 10 mg. per cent, the urea clearance, 60 per cent of normal. Blood alkaline phosphatase, bilirubin, thymol turbidity and cephalin flocculation tests were normal. Bromsulphalein retention was 14.6 per cent of the administered dose (5 mg./kg.) after forty-five minutes. An electrocardiogram revealed right bundle branch block. Chest

films and fluoroscopy demonstrated enlargement of the left and right atria and right ventricle.

Cardiac catheterization (Table II) revealed marked reduction of the cardiac output at rest with failure to increase during exercise. Although pulmonary "capillary" and pulmonary artery pressures were only moderately increased at rest, they rose considerably during exercise. The mitral valve area was estimated as 1.2 sq. cm. A mean gradient across the tricuspid valve during right ventricular diastole of 2.9 mm. Hg at rest and 5.6 mm. Hg during exercise was observed. Despite the calculated tricuspid valve area of 1.2 sq. cm. there was some uncertainty about the significance of the lesion and it was decided to perform only a mitral valvuloplasty. At operation on March 23, 1954, the mitral valve was found to be severely stenosed without regurgitation. The orifice was estimated as less than 1 sq. cm. and was substantially increased following fracture of the medial commissure. Aschoff's bodies were not detected in the biopsied atrial appendage.

Postoperative convalescence was slow. Atrial fibrillation became the established cardiac rhythm. Over the next three years there was no improvement. The patient was very fatigued, dyspneic, orthopneic and suffered from persistent edema which required the administration of bi-weekly mercurial diuretics. A murmur of tricuspid insufficiency was first detected after the onset of atrial fibrillation. One year postoperatively a diminuendo diastolic blowing murmur along the left sternal border was first noted. The patient's failure to improve prompted her readmission.

The pulse was irregular at a rate of 60. Blood pressure was 128/82 mm. Hg. The lungs were clear. There were prominent systolic pulsations in the neck veins. The liver also pulsated with systole and was enlarged two fingerbreadths below the costal margin. The heart was slightly enlarged to the right and left. At the

apex the first sound was soft and there was no opening snap. A grade 1 faint mid-diastolic rumble which faded with inspiration could be heard at the apex only with the patient in the left lateral position. In the fourth intercostal space 7 cm. from the midsternal line were a coarse systolic thrill and a fine purring

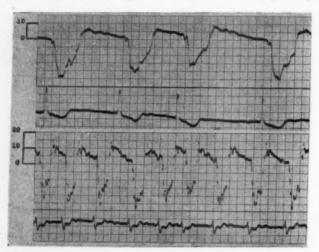


Fig. 8. Difference between pressures in right atrium and ventricle recorded from double-lumen catheter via differential manometer\* simultaneously with electrocardiogram in patient R. P. with atrial fibrillation, tricuspid stenosis and insufficiency. Upward deflection from zero line occurs when atrial pressure is greater than ventricular; downward deflection indicates converse. Calibration in this and subsequent tracings in mm. Hg. At rest (upper strip, record speed, 50 mm./second) atrioventricular gradient is large early in diastole, subsequently diminishes and disappears at the end of long diastolic intervals. During exercise (lower strip, record speed, 25 mm./second) gradient increases and is sustained throughout diastole.

diastolic thrill with a corresponding grade 3 blowing systolic murmur and a grade 2 mid-diastolic rumble, both of which increased in intensity with inspiration. The increase in the intensity of the diastolic murmur was particularly striking. A grade 1 systolic murmur was detected at the aortic area and was accompanied by an intermittent systolic thrill in the carotid arteries. A grade 2 diastolic decrescendo blow could be traced from the aortic area down the left sternal border.

Chest roentgenograms, cardiac fluoroscopy, electrocardiograms (aside from atrial fibrillation) and routine laboratory data were similar to those obtained preoperatively. A second cardiac catheterization (Table II) performed on April 12, 1957, revealed further reduction of cardiac output, and some increase in pulmonary vascular resistance. The gradient across the tricuspid valve (Fig. 8) with the patient at rest had increased slightly. The calculated mitral valve area was similar to the previous figure, but the reliability of the estimation in the presence of aortic regurgitation was questionable. The pressure pulse of mitral

insufficiency was present in the pulmonary "capillary" pressure tracing and that of tricuspid insufficiency in the right atrial tracing. The presence of tricuspid insufficiency was demonstrated further by the appearance of T-1824 dye in the right atrium as it was injected into the right ventricle at a constant rate. By a technic developed in this laboratory the regurgitant flow was calculated to be only 0.22 L./minute. The calculated area of the tricuspid valve orifice was slightly smaller than previously. The brachial artery pressure curve showed an anacrotic slur, a late systolic peak and a rapid fall to the incisura compatible with aortic valve deformity.

Comment: Failure of this patient to improve following mitral valvuloplasty could be attributed to a number of factors including inadequate mitral widening, resealing of the commissures and the presence of aortic and tricuspid involvement. The patient continued to be troubled by fatigue and edema. On the basis of the hemodynamic data re-exploration of the mitral valve and a simultaneous tricuspid valvuloplasty have been recommended. The possibility that associated valvular lesions may influence the postoperative course after mitral valvuoplasty must be borne in mind. Yu and co-workers [11] studied a patient with combined mitral and tricuspid stenosis who did not improve after mitral surgery until a second operation relieved the tricuspid obstruction.

Clinical and hemodynamic evidence [24] of tricuspid insufficiency was detected only after the change in rhythm to atrial fibrillation. The measured rate of tricuspid regurgitation indicates that the insufficiency contributed relatively little to the hemodynamic alterations. It is of interest that the levels of cardiac output both at rest and during exercise were lower with atrial fibrillation than with sinus rhythm. It is possible that the loss of a powerful atrial contraction when atrial fibrillation develops in patients with tricuspid stenosis might result in reduction in filling of the right ventricle and lead to a lower cardiac output even though the ventricular rate is well controlled [15].

Case IV. R. R., a forty-two year old white house-wife, has been followed up at the New York Hospital since 1939. A heart murmur had been recognized at age fifteen. During her only pregnancy at age twenty-six, fatigue, shortness of breath and edema had first appeared, and atrial fibrillation became established. Digitalis was administered and following delivery her condition had improved. Intermittent edema reappeared at age twenty-eight. By age thirty-two dyspnea

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<sup>\*</sup> Sanborn differential transducer, Model 467B.

on ordinary exertion was prominent. Orthopnea had been present since age thirty-four. Hepatomegaly had first been detected one year later. Since age thirty-six she has never been free of edema. Severe edema and acute respiratory infections have necessitated repeated hospital admissions. Since age thirty-nine she has worn maternity clothes because of persistent ascites, and has had a paracentesis every three to five weeks. Treatment has included a low salt diet, administration of digitalis, tri-weekly mercurial diuretics, ammonium chloride and oral cation exchange resins. Cardiac catheterization was performed in 1951 and repeated in February, 1955. At the time of the second catheterization fatigue and shortness of breath were precipitated by light household activity, and she required three to four pillows when in a supine position because of orthopnea.

She was a thin, chronically ill, white woman who would not lie flat. Blood pressure was 115/75 mm. Hg. Atrial fibrillation at a slow ventricular rate was present. There was marked edema to the mid-chest, and ascites. The external jugular veins were distended to the angle of the jaw and pulsated in systole. The liver was enlarged and also pulsated in systole. The heart was enlarged to the right and the left with a heaving apical impulse in the anterior axillary line. There were systolic and diastolic thrills at the apex, a separate, purring, diastolic thrill midway between the apex and sternum in the fifth intercostal space, and a systolic thrill in the aortic area. The second pulmonic sound was accentuated; the aortic sound was muffled. In the mitral area the first sound was obscured by a grade 3 mid-diastolic rumble. In the aortic area grade 2 murmurs of aortic stenosis and insufficiency were present. Four centimeters to the left of the sternum in the fifth interspace a grade 3 harsh systolic murmur was followed by a grade 4 roaring diastolic murmur of higher pitch than the murmur at the apex. During inspiration the murmurs in the tricuspid area increased in intensity; those at the apex decreased.

Electrocardiograms have shown no axis deviation, a qR complex in V1, deep Q waves in V2 and V3 and tall R waves in V5 and V6. Roentgenograms of the heart, including angiocardiograms, defined enlargement of all four cardiac chambers with a huge right atrium. The first cardiac catheterization revealed a cardiac index of 2.28 L./minute/M2, severe pulmonary "capillary" and right atrial hypertension, but only moderate elevation of pulmonary arterial pressures. A 6.6 mm. Hg gradient across the tricuspid valve during right ventricular diastole was diagnostic of tricuspid stenosis. The pattern of tricuspid insufficiency was present in the right atrial pressure curve. Similar data were obtained during a second catheterization thirty-nine months later but the catheter could not be passed into the pulmonary artery. Laboratory data included: hematocrit, 41 per cent; bilirubin, 1.2 mg. per cent; albumin/globulin, 3.8/1.5 gm. per cent; serum cholesterol, 155 mg. per cent; urea clearance, 35 per cent of normal.

Comment: This is one of the six patients in the present series in whom recurrent edema was a therapeutic problem. Chronic venous hypertension, hepatomegaly and ascites were common to all. In these patients, especially the three with recurrent ascites, a diagnosis of tricuspid stenosis might have been suggested on the basis of history alone [7], but could be made with assurance in five after detection of a characteristic diastolic murmur and thrill in the tricuspid area. It is noteworthy that dyspnea and orthopnea were prominent symptoms and were pronounced in the presence of severe edema.

In this group it is difficult to isolate the symptoms and hemodynamic abnormalities due to the tricuspid stenosis from the other valvular manifestations. Four patients had aortic valvular lesions. All had atrial fibrillation, tricuspid insufficiency, as well as mitral stenosis and insufficiency with consequent pulmonary venous hypertension, increased pulmonary vascular resistance and pulmonary arterial hypertension. The chronic, severe systemic venous hypertension, a significant factor in the recurrent edema [22,23], which is often considered characteristic of tricuspid stenosis [7], was not a reflection of the tricuspid stenosis alone. Right ventricular failure and tricuspid regurgitation also contributed significantly to the pronounced elevation of the right atrial pressures. Indeed, this combination of factors was associated with the highest resting mean right atrial pressures encountered.

Case v. R. G., a twenty-three year old white extruck driver, was admitted to the New York Hospital on January 25, 1957. He had no history of rheumatic fever. A murmur had been detected at the age of twelve. Easy fatigability appeared when he was nineteen. Two years before admission, in the hope of improving his cardiac function, a talcum powder cardiopexy had been performed at another hospital. Postoperatively severe right heart failure had developed, he had gained 23 pounds and had required digitalis and mercurial diuretics. Thereafter he had been unable to work and had suffered from bouts of rapid palpitation. Eighteen months before admission, cold feet and absence of the dorsalis pedis pulses were noted after an episode of aching pains in his thighs and calves. Orthopnea and dyspnea had first appeared three months before entry in association with cough, pain in the right upper quadrant, increase in abdominal girth and pedal edema. At the

time of admission he complained of chronic fatigue, he could not sleep in a flat position, and was unable to walk more than one block or climb one flight of

stairs slowly without dyspnea.

The patient appeared chronically ill. His pulse was 88 and regular. The external jugular veins were not prominent; they appeared constricted and could be palpated as tense cords, which pulsated slightly but not abnormally in presystole and asystole. There were inspiratory rales at both lung bases. The liver was four fingerbreadths below the costal margin, tender and pulsated in presystole. There was moderate pretibial edema. Dorsalis pedis pulses could not be felt. The heart was enlarged to the left and right. There was a striking left parasternal heave. A presystolic thrill was palpated at the apex and another 4.5 cm. from the left sternal border in the fourth anterior intercostal space. A systolic thrill was present one interspace below the tricuspid diastolic thrill. An intermittent systolic thrill was present over the carotid arteries. A grade 3 mid-diastolic-presystolic murmur at the apex decreased on inspiration and increased on expiration. In the tricuspid area a grade 2 middiastolic-presystolic rumbling murmur, which was transmitted to the aortic area, was followed by a grade 3 shrill, blowing systolic murmur transmitted to the apex. Both tricuspid murmurs increased during the first phase of a deep inspiration. A grade 2 diastolic diminuendo murmur, which was readily separated from the other diastolic murmurs by its higher pitch, could be traced from the aortic area down the left sternal border.

An electrocardiogram showed right axis deviation, peaked and bifid P waves of increased duration and amplitude (Fig. 5) and an rsR' pattern in lead V<sub>1</sub> with a QRS time of 0.10 seconds. Chest films and fluoroscopy revealed large left and right atria, enlargement of the right ventricle and possibly of the left ventricle.

Cardiac catheterization (Table 11) demonstrated a gradient across the tricuspid valve during right ventricular diastole of 10.7 mm. Hg at rest and 15.6 mm. Hg during exercise. (Fig. 8.) The resting pulmonary "capillary" pressure was greater than plasma protein osmotic pressure. Cardiac output was markedly reduced and did not increase with exercise. Pulmonary vascular resistance was only minimally increased. Mean right atrial pressure increased from 12 to 22 mm. Hg during exercise. The peak-plateau pattern of tricuspid insufficiency was apparent in the right atrial pressure tracing. Tricuspid regurgitation was further demonstrated by the appearance in the right atrium prior to recirculation of T-1824 dye as it was being injected into the right ventricle at a constant rate. The rate of regurgitation was estimated to be 1.95 L./minute at rest. The tricuspid orifice area was calculated with due consideration to the regurgitant flow as 1.1 and the mitral as 0.6 sq. cm.

The patient's course in the hospital was complicated by frequent episodes of peripheral and pulmonary edema. On the forty-ninth hospital day intractable pulmonary edema with cyanosis and hypotension developed and the patient died.

At autopsy the heart weighed 690 gm. There was a generalized adhesive, non-constrictive pericarditis secondary to talcum powder granulomata. Both atria were greatly dilated and hypertrophied. The right ventricle was 7 mm. and the left 14 mm. in thickness. The slit-like orifice of the calcified and severely stenotic mitral valve measured 1.0 by 0.2 cm. There was severe involvement of the commissures and chordae. The tricuspid valve leaflets were moderately thickened and fused to form an oval orifice 1.1 sq. cm. in area. (Fig. 7.) The chordae tendineae were only slightly involved. The aortic leaflets were fused at the edges and rolled, but the orifice easily admitted one finger. The aortic valve would not hold a water column in the aorta. The myocardium contained a patchy fibrosis without Aschoff's bodies. The coronary arteries were normal. The lungs were edematous and the liver was passively congested.

Comment: This is the only patient in the series with normal sinus rhythm who had associated tricuspid insufficiency. (Fig. 8.) In one other, R. P., clinical and physiologic evidence of tricuspid insufficiency developed only after the onset of atrial fibrillation. All patients with atrial fibrillation had tricuspid insufficiency. Tricuspid insufficiency in patients with chronic rheumatic heart disease and normal rhythm is uncommon. In atrial fibrillation, however, the "peak-dome" rise in right atrial pressure diagnostic of tricuspid regurgitation is almost invariably present [24].

In patient R. G. the tricuspid insufficiency was secondary to the severe valvular deformity. The leaflets were held apart centrally and could not have closed properly during ventricular systole. (Fig. 9.) The rate of regurgitation was about 50 per cent of the cardiac output and thus comprised one-third of the total volume ejected by the right ventricle. The diastolic gradient across the valve and the right atrial pressure were significantly greater than they would have been without the regurgitation. This is the second reported instance in which the calculated tricuspid orifice compared favorably with the value obtained by "planimeterizing" a scale postmortem photograph of the valve [25]. (Fig. 7.)

Whether or not the talc pericarditis contributed to the patient's death is open to speculation although right-sided heart failure first appeared postoperatively. There was no evidence by either cardiac catheterization or autopsy that the ventricles were constricted during diastole. On

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the other hand, a beneficial effect of the cardiopexy on cardiac function could not be identified. Direct attack on the valve deformity, is at present the only rational surgical procedure.

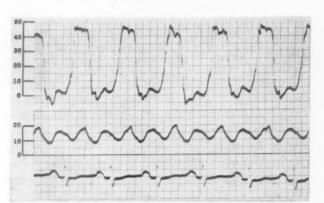


Fig. 9. Simultaneously recorded right ventricular (upper), right atrial (middle) pressures and electrocardiogram (lower) in patient R. G. with tricuspid stenosis, insufficiency and sinus rhythm. Record speed: 50 mm./second. Right atrial pressure exceeds right ventricular pressure throughout diastole; gradient is maximum during atrial contraction. Double-peaked pressure wave in atrium during ventricular systole is due to tricuspid regurgitation.

#### COMMENTS

With the exception of pulmonic stenosis, which is extremely rare, stenosis of the tricuspid valve is the least common of the rheumatic valvular lesions. Nevertheless, the lesion is not rare; in several large series of autopsy cases of rheumatic heart disease the incidence varied from 7.5 to 9.4 per cent [9,27,28]. It is not certain that all these lesions were hemodynamically significant. Clinically the recognition of tricuspid stenosis has been hampered by difficulty in identifying murmurs originating from the tricuspid valve. This has been due to confusion about the location of the auscultatory area of the valve on the precordium, as well as to inability, until recently, to confirm or reject the diagnosis except by autopsy.

Rivero Carvallo's demonstration that the murmurs of tricuspid stenosis [29] and insufficiency [30] increase with inspiration and decrease with expiration has proved very useful for the identification and differentiation of these murmurs from those due to other causes. This respiratory maneuver is especially valuable in detecting tricuspid stenosis [29] since the lesion is almost invariably accompanied by mitral stenosis, the murmur of which may be confused with that of the tricuspid lesion, especially if the

heart is small. In eleven of the twelve patients in the present series a diastolic murmur and accompanying thrill, which were present in the third, fourth or fifth left intercostal space

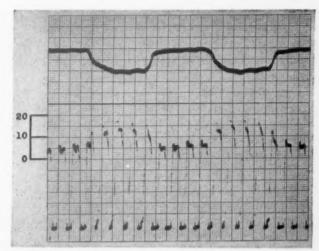


Fig. 10. Simultaneously recorded intraesophageal pressure (upper) and differential pressure across tricuspid valve (lower). Record speed: 10 mm./second. Differential pressure record reads as in Figure 7. During forced inspiration (fall in intraesophageal pressure) diastolic pressure gradient across valve increases strikingly and decreases during expiration.

parasternally and increased in intensity with inspiration, proved to be reliable evidence of tricuspid obstruction. In all those with accompanying lesions of the mitral valve the murmurs of mitral stenosis and insufficiency decreased with inspiration and increased with expiration.

The difference in the timing of the diastolic murmur of tricuspid stenosis in sinus rhythm and atrial fibrillation correlates with the variation in the gradient from the right atrium to right ventricle during right ventricular diastole [15]. In normal sinus rhythm the gradient is small until the onset of atrial contraction, which is of unusually high amplitude. (Fig. 9.) In these patients, in contrast to those with unobstructed atrioventricular valves in whom atrial contraction contributes little to ventricular filling [30,31], a larger portion of ventricular inflow and the greatest transvalvular flow rate and turbulence of the blood stream probably occur during atrial systole when the gradient is maximal. Hence the murmur is most intense in presystole. In atrial fibrillation, on the other hand, the gradient is maximal during early diastole and gradually diminishes. (Fig. 8.) Indeed, at the end of a long diastolic interval

right atrial and ventricular pressures may become equal and the gradient may disappear. (Fig. 8.) In atrial fibrillation most rapid ventricular filling undoubtedly occurs in early diastole when the gradient is largest. Thus the murmur with atrial fibrillation is maximal in early diastole, subsequently decreases in intensity and may disappear prior to the first sound, especially when the diastolic interval is prolonged.

Diastolic murmurs originating at the tricuspid valve are not invariably due to tricuspid stenosis. They have been recorded in patients with tumors of the right atrium [32] and in the presence of atrial septal defects. In a reported instance of "functional tricuspid stenosis" there were a typical diastolic tricuspid murmur and thrill, which increased during inspiration. The patient had primary pulmonary hypertension and tricuspid insufficiency, and at autopsy tricuspid obstruction could not be demonstrated [33]. Muller and Shillingford [34] have also encountered diastolic murmurs in patients with tricuspid insufficiency uncomplicated by stenosis. In our experience the occasional "functional" tricuspid diastolic murmur, such as occurs in atrial septal defect, is a mid-diastolic rumble of low intensity and short duration and would not be confused with the murmur of organic stenosis which is louder, coarser, higher pitched, longer and seems closer to the ear.

In case reports from the older literature the area for auscultation of the tricuspid valve has been located at the lower end of the sternum [9,35,36] or to the right of the sternum [6,37–39]. Only occasionally was it located correctly to the left of the sternum [10,11,27,40]. These erroneous impressions, promulgated repeatedly in textbooks of physical diagnosis [41–43], have been a source of great confusion in the detection of tricuspid valvular lesions by physical examination.

In the cadaver, a horizontal section at the level of the third intercostal space and the sternum anteriorly and the eighth thoracic vertebra posteriorly will transect the tricuspid valve [44]. In the normal frontal angiocardiogram the tricuspid valve is at the level of the third to fourth anterior intercostal space within the shadow of the vertebrae [45]. Enlargement of the right atrium alone, as demonstrated in patient F. C. with isolated tricuspid stenosis (Fig. 1), displaces the tricuspid valve to the left. Enlargement of the left atrium and especially

of the right ventricle displaces the right side of the heart and the tricuspid valve to the left. Thus, in tricuspid stenosis, since the lesion produces right atrial enlargement and is almost invariably accompanied by mitral stenosis with enlargement of the right ventricle and left atrium, the valve is displaced to the left parasternal region. (Fig. 4.) Consequently the tricuspid area in the eleven patients in whom murmurs and thrills were detected was to the left of the sternum between the midclavicular line and the sternal border. (Fig. 2.) In no case was the murmur maximal over the sternum, at the xiphoid or to the right of the sternum. Correct identification of the tricuspid area is essential for correct diagnosis of tricuspid disease.

Many criteria for diagnosis have been proposed, but most, aside from the signs elicited by auscultation and palpation, cannot be regarded as reliable evidence of tricuspid obstruction. A giant A wave of atrial contraction in the external jugular veins, which was noted in only four patients in the present series, is not diagnostic [39] since it occurs also when the diastolic pressure in the right ventricle is elevated, as in right ventricular failure and severe right ventricular hypertension. Such pulsations are a sign of increased atrial pressure, but, as was recognized by Duroziez [5], not necessarily tricuspid obstruction. Vigorous venous pulsations are also seen in constrictive pericarditis and may not be substantially different in form from the pulsations noted in combined tricuspid stenosis and insufficiency with normal sinus rhythm.

Whether or not forceful atrial contraction waves are visible in the jugular veins will depend on the ease with which the veins are visible as well as their distensibility. In patient F. C. moderate obesity of the neck obscured the veins and pulsations were not visible despite an atrial contraction reaching 14 mm. Hg. In patient R. G. the peripheral veins appeared contracted and small and only minor A and V waves were visible despite their large amplitude in the atrium. (Fig. 8.) A tall atrial contraction wave in the neck veins followed by a V wave of small amplitude with slow descent from its peak is regarded by Gibson and Wood [13] as a pathognomonic sign of tricuspid stenosis. Its presence should prompt a careful search for other signs of the disease.

The association of minimal pulmonary symptoms with advanced rheumatic heart disease has been mentioned repeatedly as evidence of tri-

cuspid stenosis [6,7,9]. However, dyspnea was present in every patient in the present series, and several had severe orthopnea. Similar observations were made in a group of patients with multivalvular rheumatic heart disease and tricuspid stenosis many years ago by Duroziez [5]. In patients without pulmonary venous hypertension, but with low and fixed cardiac outputs, the dyspnea may be related to fatigue of respiratory muscles, especially during exercise when blood flow can not be increased to meet the needs of increased muscular work. In the patients with pulmonary venous hypertension, the orthopnea and paroxysmal dyspnea are probably related to the consequent disturbances of pulmonary function and alterations in the physical properties of the lungs [46,47].

Tricuspid valvular lesions often have been assumed to "protect" the pulmonary vascular bed from the development of high levels of pressure. Sepulveda and Lukas [24] demonstrated, however, that pressures in the pulmonary vascular bed were higher in a group of patients with mitral stenosis and tricuspid insufficiency than in a similar group who did not have tricuspid insufficiency. It was concluded that patients with rheumatic heart disease who have tricuspid insufficiency have more advanced heart disease and alterations in the pulmonary vascular bed than those in whom this lesion has not developed, but it could not be stated that the pulmonary pressures might not have been even higher were there no tricuspid insufficiency.

On the other hand, Killip and Lukas [15] found that the cardiac output, pulmonary vascular pressures and resistance were lower in a small group of patients with tricuspid and mitral stenosis than in a group with isolated mitral stenosis of comparable severity. The pulmonary "capillary" pressures and the cardiac outputs in several patients with mitral and tricuspid stenosis reported by Yu and co-workers [11], and Reale and co-workers [14] were definitely lower than in patients with mitral stenosis without tricuspid obstruction. Such a "protective" action of tricuspid valve obstruction may have paradoxical effects. Although the dangers of pulmonary edema and progressive pulmonary vascular alterations secondary to mitral disease are reduced, the restriction of cardiac output may be severe and may give rise to incapacitating fatigue and retention of salt and water. In the individual patient the

functional role of tricuspid stenosis will depend on the degree of obstruction in relation to the severity of the associated valvular lesions. It is apparent that considerable pulmonary venous and arterial hypertension may develop secondary to severe mitral and aortic valvular disease in the presence of "tight" tricuspid stenosis.

Shattuck's dictum stressing edema [7] as an aid to the clinical diagnosis of tricuspid stenosis has been repeated by many observers [6,9,37]. This emphasis on fluid retention has been due to failure to diagnose the lesion early and to the advanced devolution characteristic of the patients studied at autopsy. If to the increase in right atrial pressure that is produced by right ventricular failure with raised right ventricular diastolic pressure be added the systolic pressure rise of tricuspid insufficiency and the diastolic gradient required to maintain flow across an obstructed tricuspid valve, the result is a marked, chronic venous hypertension. Such a combination occurs relatively late in the natural history of the disease; signs of the lesion are invariably present prior to the development of edema.

There is increasing evidence of the importance of venous hypertension in the salt and water retention of right-sided heart failure. Unilateral constriction of a renal vein produces sodium and water retention in the dog [23]. In man, obstruction in many portions of the venous bed leads to similar changes [48,49]. Hollander and Judson found that in patients with rheumatic heart disease and right ventricular end diastolic pressures greater than 15 mm. Hg at rest edema developed and they gained weight when given increased salt and water loads, whereas those with end diastolic pressures below this level were able to excrete the increased load normally [22]. Retention of salt and water in patients with tricuspid stenosis is a reflection of chronic venous hypertension, and probably of diminished renal blood flow. High venous pressures are encountered in a variety of heart diseases as well as in combined tricuspid stenosis and insufficiency, and do not necessarily reflect the severity of the tricuspid stenosis. Failure to appreciate the various factors which determine the level of venous pressure in tricuspid stenosis, the degree of valvular obstruction being only one, has led to overemphasis of the diagnostic importance of marked venous hypertension in the lesion.

Conspicuous right atrial enlargement in rheu-

matic heart disease should suggest the possibility of tricuspid stenosis and motivate a diligent search for evidence of the lesion on physical examination. This is especially true with normal sinus rhythm, since a common cause of right atrial enlargement, tricuspid insufficiency, is notably less frequent in normal rhythm than in atrial fibrillation [24]. Angiocardiograms demonstrating prolonged opacification of the right atrium and a sharply outlined atrioventricular border are most suggestive of tricuspid obstruction. (Fig. 4.) The prolonged clearance of contrast material from the atrium is due to the small stroke volume/atrial volume ratio and the greater radiopacity of dilute concentrations of contrast material within a large as compared to a small chamber.

Tall, peaked P waves in the electrocardiogram of patients with rheumatic heart disease should suggest the possibility of tricuspid stenosis. (Fig. 5.) This sign, reflecting right atrial hypertension and secondary hypertrophy and dilatation, has also been encountered in tricuspid insufficiency and in right ventricular failure without a tricuspid lesion, and is not specific. Small QRS complexes especially of rsr' pattern, in  $V_1$  or  $V_2$  and of lower amplitude than the associated P wave (Fig. 6) are also very suggestive of tricuspid stenosis.

Smith and Levine [27] in a retrospective autopsy study found that patients with tricuspid stenosis complicated by aortic or mitral stenosis survived longer after the onset of heart failure but had an average age at death that was lower than those without tricuspid stenosis. However, the effect of tricuspid obstruction on the prognosis of rheumatic heart disease must remain speculative since so few cases have been followed up for any prolonged period during life. The reduction of cardiac output consequent to significant obstruction probably retards the progressive restriction of the pulmonary vascular bed and progressive pulmonary arterial hypertension which is so characteristic of mitral stenosis and which reduces the left ventricular load in aortic stenosis. On the other hand, the increasing edema formation as the disease advances and the severe fatigue and poor exercise tolerance result in progressive disability and pose most difficult therapeutic problems.

The pathologic alterations in the tricuspid valve in the two patients in whom autopsy was performed were similar to those that have been reported by others [5-7,27,28,35-40]. The major

deformity is a fusion of the commissures, which are difficult or impossible to identify. The cusps are only moderately thickened and are pliable: The chordae tendineae are not severely deformed and do not produce subvalvular stenosis as they do often in mitral valvular disease. The orifice is generally oval and insufficient as well as stenotic [50]. The short funnel-shape of the deformed valve is probably influenced by the insertion into each leaflet of chordae from two of the three papillary muscles. Thus the pull of the chordae on the edge of the valve is in three opposing directions [50]. As noted by Bertin [3], calcification of the valve is uncommon; none was demonstrated roentgenographically in our patients. The mitral valve is almost invariably more stenotic than the tricuspid, and involvement of the aortic valve is frequent [5,9,27,50]. Herrick stated sixty years ago that tricuspid stenosis does not occur with aortic stenosis alone [37]; to date no such instance has been reported. There has been only one case report of combined mitral and tricuspid stenosis in which the tricuspid orifice was smaller [51]. Clements [52] reported a case of tricuspid stenosis with wide open mitral insufficiency. In the rare instances of isolated tricuspid stenosis the pathologist often has difficulty deciding whether the lesion was congenital or acquired.

With careful attention to the details of the physical examination, especially the respiratory variations of the murmurs, and with the information derived from the electrocardiogram and roentgenography of the heart, a diagnosis of tricuspid stenosis is possible in a high percentage of instances. If the lesion is suspected, catheterization of the right side of the heart with complete studies at rest and during exercise is the most useful procedure for confirming the diagnosis, and assessing its physiologic significance. Right ventricular and right atrial pressures should be obtained at high sensitivity and the recordings carefully analyzed since the drop in pressure across the valve during diastole may be only a few millimeters of mercury [15]. During exercise the gradient invariably increases. When tricuspid stenosis is associated with mitral stenosis, and mitral valvuloplasty is contemplated, serious consideration should be given to exploring the tricuspid valve during the procedure. Because of the danger of sudden increases in pulmonary flow it is advisable to fracture the most distal valve first. Uncorrected tricuspid stenosis may obscure the beneficial effect of

successful mitral valvuloplasty and may be the cause of persistent disability.

#### SUMMARY

Tricuspid stenosis was identified clinically and confirmed by cardiac catheterization in twelve patients. In one patient the lesion was isolated. It was associated with mitral disease in four, and with both aortic and mitral lesions in seven. Two patients came to autopsy and two underwent tricuspid valvuloplasty.

The most striking clinical feature was a characteristic diastolic murmur with a thrill in the third, fourth and fifth intercostal spaces to the left of the sternum. The increase in intensity of the murmur during inspiration and the decrease during expiration aided greatly in identifying the murmur and differentiating it from that of mitral stenosis. The intensity of the murmur varied with respiration in the same manner as the transvalvular diastolic pressure gradient. An opening snap of the tricuspid valve was heard in only three cases. Dyspnea, fatigue and edema were the most common symptoms but the resulting disability was quite variable. Recurrent ascites was present in three patients.

The right atrium was enlarged in every patient but was massive in only three. The largest right atria, the most severe right atrial hypertension and the greatest tendency to develop edema were associated with coexisting tricuspid insufficiency, multivalvular disease and atrial fibrillation. Tall P waves, often taller than QRS in V<sub>1</sub>, and low QRS complexes with an rsr' pattern in lead V<sub>1</sub> were common features of the electrocardiogram.

In one patient the area of the tricuspid orifice estimated from data obtained at cardiac catheterization and that determined by planimetery of a postmortem photograph of the valve were identical. In two patients in whom autopsy was performed the tricuspid valve was less stenotic and deformed than the mitral valve.

The pulmonary vascular pressures and resistance in patients with mitral and tricuspid stenosis were lower than in patients with a similar degree of mitral stenosis alone. Pulmonary venous hypertension, however, was not entirely prevented and most of the patients had pulmonary congestive symptoms of mitral stenosis, including orthopnea. The failure of one patient to improve following mitral valvuloplasty was attributed to the tricuspid stenosis.

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## Estimation of Severity of Aortic Stenosis by Combined Heart Catheterization\*

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THE advances in the surgical treatment of a aortic stenosis have necessitated a more precise objective evaluation of this disease. This is desirable from a standpoint of an estimation of the severity of the lesion preoperatively, which will form a basis for selection of patients, as well as improvement postoperatively. Catheterization of the left side of the heart [1,2] provides a method for the measurement of the altered pressure relationships in the left heart chambers and aorta. When combined with an estimation of the flow across the valve, this procedure permits an accurate assessment of the degree of obstruction and work load of the left ventricle, hitherto impossible [3]. Accordingly, we have employed simultaneous catheterization of the left and right side of the heart to record the pressure-flow relationships in a series of patients with clinically pure aortic stenosis. The physiologic data provide the material for this report.

#### MATERIAL AND METHODS

Thirty-seven patients with clinically pure aortic stenosis were evaluated. All but one were considered to have the lesion on the basis of rheumatic fever. In one patient, aged eighteen, with a history of a murmur since birth, it was congenital in origin. The lesion was confirmed in thirty-six cases at surgery and in one at autopsy.

The method of study is detailed in a previous communication [4]. Pre-medication consisted of seconal® 0.2 gm., and demerol,® 50 mg. Catheterization of the right side of the heart was performed in the usual way except that the patient lay in the prone position. After recording the pulmonary artery wedge pressure, the catheter was withdrawn and the tip positioned in the pulmonary artery. A Cournand needle was placed into the brachial artery. In some patients a radiopaque catheter was advanced in a retrograde manner into the ascending aorta through the brachial artery. A

No. 6-18G thin walled needle was then introduced into the left atrium according to the Fisher [5] modification of the Bjork [6] technic. A polyethylene or nylon catheter was inserted through the needle and advanced into the left ventricle while continuous monitoring of the intracardiac pressures and electrocardiogram on an oscilloscope was made. When the left ventricle was entered, all maneuvering was halted except in those patients in whom a deliberate attempt to enter the aorta was made. As soon as the control rate, rhythm, and blood pressure were re-established, expired air was collected in a Tissot spirometer for three minutes. In the middle of this period, blood samples were withdrawn from the pulmonary artery and brachial artery (or aorta). Pressures were then recorded from the left ventricle and brachial artery (or aorta) simultaneously to obtain the left ventriclebrachial artery (or aorta) pressure gradient. Pressures were then recorded as the catheter in the left side of the heart was withdrawn from the left ventricle to the left atrium. Simultaneous recordings were then made of the pulmonary wedge and left atrial pressures.

Pressure recordings were made in the earlier group employing electromanometers (Sanborn) and recording on a polyoscillograph (Sanborn). In the latter group, P-23D Statham strain gauges were used in conjunction with the Research Recorder (Electronics for Medicine). This provides a method for simultaneous recording of the pressures with gauges of equal sensitivity employing a common baseline.

The cardiac output was calculated by the direct Fick method. Blood oxygen was determined by the method of Van Slyke and Neill [7]. The respiratory gas analyses were made by the Pauling Oxygen Analyzer. The zero level for pressures was taken as 5 cm. from the angle of Louis. Pressure gradients were calculated by planimetric integration. Valve area, pulmonary resistance, and ventricular work were calculated by modification of the formulas of Gorlin and Gorlin [8].

A.V.A. (cm.²) = 
$$\frac{\text{A.V.F.}}{44.5 \sqrt{\text{L.V.}_{s.m.} - \text{B.A. (A)}_{s.m.}}}$$

<sup>\*</sup> From the Brith Sholom Cardiopulmonary Laboratory and the Departments of Medicine and Thoracic Surgery, Hahnemann Medical College and Hospital, and the Bailey Thoracic Clinic, Philadelphia, Pennsylvania.

† Work done during tenure of Southeastern Heart Fellowship in cardiovascular diseases.

A.V.F. (cc./S.E.P. second) = 
$$\frac{\text{C.O.}}{\text{S.E.P.} \times \text{H.R.}}$$
  
L.V.<sub>eff.w.</sub> (kg.m./minute/m.²) =  $\frac{\text{(C.I.} \times 1.055)(\text{B.A.}_{m.} \times 13.6)}{1000}$ 

L.V.t.w. (kg.m./minute/m.2)

$$\frac{(\text{C.I.} \times 1.055)(\text{L.V.}_{\text{s.m.}} \times 13.6)}{1000}$$

ular work

C.O.

A.V.A. (cm.2)	= aortic valve area
A.V.F. (cc./S.E.P. second)	= aortic valve flow
C.O. (1/minute)	= cardiac output
L.V. <sub>s.m.</sub> (mm. Hg)	= mean systolic ejec- tion pressure of left ventricle
B.A. (A) <sub>m</sub> (mm. Hg)	= mean systolic pres- sure of brachial artery (aorta)
S.E.P. (second)	= systolic ejection period (Fig. 1)
H.R.	= heart rate
L.V.eff.w.	= effective left ven- tricular work
C.I.	= cardiac index
L.V.t.w.	= total left ventric-

L.V.<sub>eff.w.</sub> refers to that portion of the left ventricular work exerted against the pressure in the aorta while L.V.<sub>t.w.</sub> refers to total work of this chamber.

150 100 50 SEP

Fig. 1. Left ventricular and aortic pressure tracings in a patient with aortic stenosis showing the systolic pressure gradient (shaded area), systolic ejection pressure (double hatched area), and systolic ejection period (SEP). Paper speed 25 mm./second.

#### RESULTS

The physiologic data are shown in Table 1. The cardiac index was low for the group as a whole averaging 2.4 L./minute/m²BS (range: 1.0 to 4.4 L./minute/m²BS). The stroke volume ranging between 25 to 86 cc. averaged 47 cc. The aortic valve flow ranged between 81 and

317 cc./S.E.P. second averaging 164 cc. (normal range 175 to 250 cc./S.E.P. second).

The systolic pressure in the left ventricle was constantly elevated. The end diastolic pressure, ranging from 2 to 44 mm. Hg, was greater than the upper limits of normal, 10 mm. Hg, in all but eleven cases. The pressure pulse showed a rapid rise to a smooth rounded peak and a slower decline after a point corresponding to the dicrotic incisura of the aortic or brachial arterial curve. In the majority of cases the peak of ventricular systole occurred earlier than the peak of systole in the peripheral pressure pulse. In about one-half of the cases, the phenomenon of mechanical pulsus alternans was observed in the left ventricular pressure pulse. This reflected itself in the central aorta or brachial artery pulse. Electrical alternans was not observed.

The total work of the left ventricle was generally increased, averaging 5.44 kg.m./minute/m² (range: 1.80 to 10.10 kg.m./minute/m²); normal range is 2.9 to 3.9 kg.m./minute/m². In an occasional case (J. Sol.) the work was below normal despite severe obstruction as a result of a marked decrease in the cardiac output.

The mean left atrial pressure was elevated reflecting the high left ventricular diastolic pressure. The pressure tracing demonstrated large "a" waves in those patients with normal sinus rhythm.

The brachial artery systolic pressure ranged between 90 and 180 mm. Hg and the diastolic from 60 to 120 mm. Hg. The pulse pressure varied between 25 and 76 mm. Hg, being generally within normal limits. The peripheral arterial pressure tracings were similar to those reported previously [9]. The majority of patients showed an anacrotic notch or slur on the upstroke with a delay in the peak of systole (range: 0.10 to 0.24 second, average 0.20 second. Normal range 0.08 to 0.12 second). In two cases the upstroke was smooth and the contour was essentially normal. The dicrotic limb was normal in all cases.

The central aortic pressure was recorded in twenty-four cases. In seventeen of these the brachial artery pressure was recorded simultaneously. The systolic pressure in the peripheral vessel was slightly higher than that in the aorta. The diastolic pressures were similar in two patients, higher in the aorta in five, and lower in the aorta in six patients. The pulse pressure was greater in the peripheral artery in all but two patients.

TABLE I AORTIC STENOSIS

			(3)	10		1		Fulm	monic Circulation			1				Systemic Circulation	Chiano							
		( 0				(1		Pressures	(mm. Hg)					Pr	Pressures (mm. Hg)	(2	1		*(8H		(:	(gui)		
Oxygen Consumption	(cc./min./m²BS)	Difference (vol. %)	Cardiac Output (L./min	Cardiac Index (L./min./	Heart Rate (beats/min.)	Stroke Volume (cc./bear	Right Atrium (mean)	Right Ventricle	Pulmonary Artery	Pulmonary Capil-	Pulmonary Vascular Re- sistance (dynes sec. cm.	Right Ventricular Work (kg.m./min.)	Left Atrium (mean)	G\S ələiriαəV flə.I	(nesm) G\S smoA	Brachial Artery S/D (meam)	Left Ventricular Ejection (mean)	Systolic Ejection Period (sec./beat)	LV-BA Gradient (mm. I	Aortic Valve Flow Co., SEP sec.)	Aortic Valve Area (cm. <sup>8</sup>	Left Ventricular Work Effective (kg. m./min./	Left Ventricular Work, Total (kg. m./min./m²	Left Ventricular Stroke Work (gm. m./min./m
	04 4.	6.5	4 6	rn 00	64 5	53	10	25/15	30/14(20)	10	182	0.66	10	188/18		110/80(86)	165	.28	67	128	0.0	2.84	4.5.4	5 98 35
Z. 1		0.4	0 0	ru a		42	- 4		22/15(20)	14:	40 0.	0.72		214/24	100/90(95)	104/62(80)	143	.28	75	148	0.4	200	10.4	14 54
· ·		000	2 2 2	0 00		99	0		21/10(13)	9	138	0.52		197/10	96/60(74)	(96)(96)	167	.32			0.5	9 60	05 6.6	
	106 10	41	0 1	0 1		56		30/5-50/10	30/15-40/20(25)	10	759	0.42		104/12-160/14	1007/07/04	120/60(78)	125	.22		116	0.0		1	
		4	30	+ 1		78	10	4/62		2	91	0.58	6	180/16	100/00(/2)	134/80(100)	169	.24			0.8	<u> </u>	88 6.5	
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S. F.	10 4	27	2 2 2	0 4		26	00	22/2	28/16(20)	8 8	1140	0.44	0 6	230/7	112/60(86)	120/60(76)	177	. 28		101	0.0	- 2	65 3.58	
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		3	6	4		44		39/8	30/15(20)	6	249	0.69		232/20	140/78(100)	140/82(105)	193	.24		193	0	3	-	
	117 6	0. 4	2	7	-	41		68/19	74/35(54)	32	593	593 1.32	28	168/18	94/70(78)	102/70(82)	150	24			000		3.6	
_	_	. 60	2 2			40	S	26/2	20/10(14)	34	2 :	0.42		190/18	104/78(86)	104/70(80)	180	.38	09		0 0		42 5.42	
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	148 9	.4	9	2	_	21	9	75/8	74/45(55)	20	1050	0	CA	170/28	108/60(74)	110/74(88)	142	.28	_	_	0		90 3.0	
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	120 6	6.6		7	-	32	15	83/20	80/35(50)	36	407	1.23		200/44		140/90(110)	159	. 28	44		0	200	9 6	
	127 5	5.5	64	.3	-	65		30/5	25/10(20)	15	2380.	99.0	6	180/16	(29)09/08	116/75(90)	148	.36			0		4	87 5
_	137   5	5.3		9.	-	25	4	40/4	40/10(22)	22		10 75		220/25		110/60(74)	161	33	_	-	-		4	_

\* Measured by planimetric integration.
† Left ventricular aortic pressure gradient.

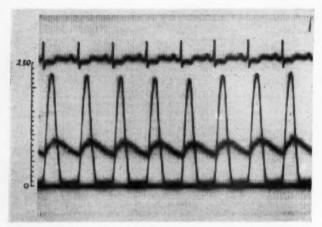


Fig. 2A. Left ventricular and aortic pressure tracings in aortic stenosis. Note systolic pressure gradient and anacrotic notches in aortic curve. Paper speed 25 mm./second.

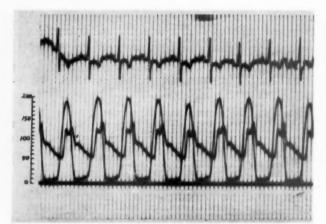


Fig. 2B. Left ventricular and brachial artery pressure tracings in aortic stenosis. Paper speed 25 mm./second.

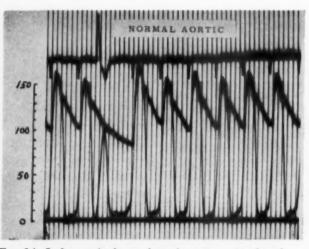


Fig. 3A. Left ventricular and aortic pressure tracings in a person with a normal aortic valve. No pressure gradient during systole. Note the ventricular premature systole (third beat) which did not produce an aortic pulse. Paper speed 25 mm./second.

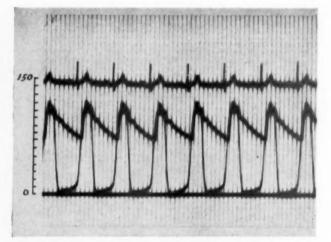


Fig. 3B. Left ventricular and brachial artery pressure tracings in a person with a normal aortic valve. Note small negative pressure gradient. Paper speed 25 mm./second.

The most constant physiologic abnormality in aortic stenosis was the presence of a pressure gradient between the left ventricle and the aorta or brachial artery during ventricular systole. (Figs. 2A and B.) Normally there is no measurable gradient during this phase of the cardiac cycle between the ventricle and aorta. (Fig. 3A.) The mean pressure gradient in this series ranged from 25 to 103 mm. Hg. The gradient was not only dependent upon the degree of obstruction but upon the rate of flow as well. Similar gradients occurred at different valve areas. However, as expected, for a given valve area the gradient varied as the rate of flow as shown in Figure 4. A small negative gradient exists between the ventricle and brachial artery (i.e., the systolic

pressure is slightly higher in the periphery than in the left ventricle in normal persons). (Fig. 3B.)

A comparison of the gradient, flows, and areas employing brachial artery and central aorta is made in Table II. In general there was good agreement between the two methods of calculation. For clinical purposes, the brachial artery may be used in conjunction with the left ventricular pressure in estimating the pressure gradient and the degree of aortic obstruction.

The calculated aortic valve area fell well below the estimated normal of 3 cm<sup>2</sup>. In all patients the aortic orifice was below 1.1 cm.<sup>2</sup>; average for the group 0.6 cm.<sup>2</sup> or 20 per cent of normal. In one patient, who died at the time of surgery, the intact heart was obtained at autopsy. The heart was perfused on a McMillan

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type cyclic perfusion apparatus [10] simulating the pressure-flow relationships obtained during life. A picture taken at the height of systole is shown in Figure 5. The actual area of the orifice by planimetric integration was 0.4 cm.<sup>2</sup> while that calculated from the hemodynamic study was 0.5 cm<sup>2</sup>.

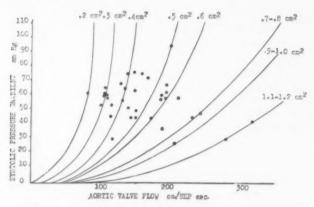


Fig. 4. Interrelationships between systolic pressure gradient and aortic valve flow in aortic stenosis for different valve areas.

The data obtained from catheterization of the right side of the heart were similar to those obtained previously [9]. The mean pulmonary artery pressures were either normal, or only slightly elevated. Several patients (E. E., H. H. and G. P.), who were in heart failure at the time of admission to the hospital but considered clinically out of failure as indicated by a constant weight under treatment with rest, digitalis, and diuretics, had severe pulmonary hypertension. The pulmonary wedge pressure was elevated above upper limits of normal in thirteen of thirty-five patients. The pulmonary vascular resistance was greater than normal in fifteen patients, markedly so in five.

#### COMMENTS

Aortic stenosis, most commonly the result of rheumatic fever but occasionally of congenital origin, tends to limit the rate of blood flow from the left ventricle. Alterations in left ventricular function take place in an attempt to maintain the aortic flow. There is a rise in the ventricular systolic pressure with the establishment of a pressure gradient across the aortic valve during systole. This pressure gradient, the sine qua non of obstruction, is a constant physiologic abnormality in this disease. The ability of the left ventricle to maintain a normal flow is related not only to the state of the myocardium but to

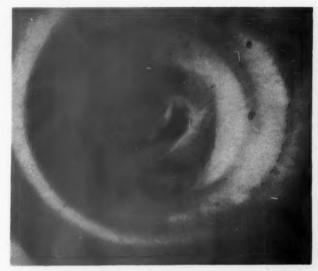


Fig. 5. Photograph of aortic valve in patient with aortic stenosis (J. Sol.) obtained at height of systole during cyclic perfusion.

the degree of obstruction. Hence, despite a compensated left ventricle, the aortic flow is frequently below normal in these patients. The inability of these patients to adequately increase the cardiac output during periods of stress was demonstrated by Goldberg and associates [9]. The tissue oxygen requirements under such circumstances are met with by increased extraction as evidenced by a widening of the arteriovenous oxygen difference.

The observed pressure gradient is not an accurate index of the degree of stenosis. The gradient is a function not only of the severity of obstruction but of the state of the myocardium and aortic blood flow as well. The influence of the latter is illustrated by Figure 4 demonstrating pressure-flow relationships for varying degrees of obstruction. Hence, measurements of the gradient alone as recommended by some observers [11] without a knowledge of the rate of flow is inadequate in the estimation of the obstruction. Similarly, the absence of a steady state due to pressure fluctuations with and without blood loss, changes in heart rate, peripheral resistance, and aortic flow preclude any accurate evaluation of direct measurements at the time of surgery. A group of patients in this series were re-studied several weeks to months following aortic commissurotomy and will be reported elsewhere [12]. A good result was considered when there was elimination or decrease of the pressure gradient accompanied by an increase in aortic flow.

In addition to a constant rise in the systolic

Table II
COMPARISON OF GRADIENTS, FLOWS, AND AREAS USING AORTA AND BRACHIAL ARTERY

Name		(mm. Hg) (mean)	Eje Pe	tolic ction riod /beat)	Valv	ortic e Flow EP sec.)	Pressure Gradient (mm. Hg)		Valv	ortic ve Area m.²)
	A	В	A	В	A	В	A	В	A	В
C. McD.	140/80(98)	142/80(94)	.30	.32	140	131	67	55	.5	.4
W. I.	100/60(72)	110/70(87)	. 32	.32	187	188	55	35	.6	.7
M. Z.	100/90(95)	104/62(80)	. 32	.28	130	148	108	75	.3	. 4
A. DiG.	108/60(70)	120/70(90)	. 26	.22	142	169	95	71	.3	. 5
M. S.	100/60(80)	120/60(80)	. 34	.27	85	108	67	59	.2	.3
G. B.	94/70(78)	102/70(82)	. 32	.24	129	172	69	42	.4	.2
S. B.	140/78(100)	140/82(105)	. 30	.24	179	193	78	57	.5	. 5
J. B.	100/70(82) 100/70(80		.32	.32	105	104	51	59	.4	.3
L. H.	120/100(110) 130/90(110) 84/60(66) 110/60(80)		.24	.27	255	232	56	43	.8	. 8
L. C.			. 33	.36	144	134	50	37	.5	.5
J. H.	108/60(74) 110/74(88)		.27	.28	82	81	69	60	.2	.2
R. M.	112/80(90) 138/70(110)		.25	.29	290	280	39	28	.7	1.2
M. H.	100/70(80)	107/65(90)	. 32	.30	154	150	60	48	.5	.5
D. C.	130/76(116)	156/80(108)	.24	.26	163	150	66	43	.5	. 5
W. W.	96/60(74)	90/60(76)	. 32	.32	212	200	90	94	.5	. 5
S. F.	110/78(86)	120/72(80)	.27	.28	218	159	107	74	.5	.5
G. D.	94/70(78)	102/70(82)	.32	.24	129	172	69	42	.4	.6
H. K.	180/120(130)	180/120(130)	.20	.20	311	317	58	40	.9	1.1
F. P.	112/60(86)	100/60(76)	.23	.26	120	101	76	64	.3	.3
M. M.	120/90(105) 140/100(110)		.29	.26	137	143	57	43	.4	.5
W. R.	80/60(70)	100/60(80)	.26	.28	200	186	79	59	.5	. 6
W. D.	96/60(76)	100/80(90)	.30	.28	130	139	57	50	. 4	. 4
Т. В.	80/60(70)	85/60(70)	.30	.30	207	194	71	61	.6	. 6
H. S.	95/70(80)	96/70(80)	.32	.30	184	194	68	67	.5	. 5

pressure, the end diastolic pressure of the left ventricle is frequently elevated. This finding could not be correlated with the presence of left ventricular failure clinically. A high diastolic pressure was observed in all patients in this series who were in heart failure at the time of admission to the hospital, but considered "compensated" clinically at the time of the catheterization study. Similarly, however, patients with small hypertrophied hearts and with minimal or no symptoms also had left ventricular diastolic pressure above normal. It would appear that alterations in the elasticity of the hypertrophied left ventricle may be responsible for the high diastolic pressure. However, the presence of subclinical heart failure cannot be excluded in these cases.

Further evidence that the high diastolic pressures in the left ventricle may be related to hypertrophy is suggested from an analysis of data obtained following aortic commissurotomy.

Although the obstruction was relieved in many cases and in two patients the pressure gradient was eliminated by surgery, the end diastolic pressure changed little. Preliminary observations indicate that acute digitalization may not lower the ventricular diastolic pressure [13].

The decreased distensibility of the left ventricle as a result of hypertrophy offers resistance to filling. This reflects itself in alteration of left atrial function as well. Examination of the pressure tracings reveal exaggerated "a" waves, indicating forceful atrial contraction. Similar observations have been made in the right atrial pressure tracings in patients with right ventricular hypertrophy due to pulmonic stenosis [14], mitral stenosis, or primary pulmonary hypertension [15].

Combined heart catheterization allows for an estimation of total left ventricular work. The latter is generally increased in aortic stenosis as expected. The influence of the cardiac output

is well illustrated by the foregoing data. Despite severe obstruction the total work of the left ventricle may be within normal limits or below when the output is low. The state of the myocardium is an important factor in this regard. The increased work performance of the left ventricle is undoubtedly related to hypertrophy. An important limiting factor of this hypertrophy is the coronary arterial system. The latter cannot increase pari passu with increase in muscle mass [16]. The coronary blood flow is therefore unable to meet the demand of the left ventricle. Prolongation of systole, and increased systolic resistance may further limit coronary perfusion [17]. Hence, the left ventricle is incapable of increasing its intraventricular pressure sufficiently to maintain a normal blood flow.

The theoretical considerations of application of the Gorlin formula to patients with aortic stenosis was discussed previously [8,18]. In the presence of regurgitation, the calculated area will be smaller than the actual size, since aortic flow as determined by the direct Fick method does not include the regurgitant flow. Hence, only patients with pure aortic stenosis were included in this study. The influence of shape is considered slight [18]. These observers have pointed out that the Gorlin formula is more applicable to stenotic orifices with turbulent flow than Poiseuille's Law as recommended by others [19].

It is interesting to note that the aortic valve orifice must be reduced to 20 or 30 per cent (0.5 to 1.0 cm.²) of its normal size (3 cm.²) before clinical symptoms appear. All patients in this series fell below 1.1 cm.², the average for the group being 0.6 cm.² This would tend to indicate that there is a critical valve area at which symptoms occur as suggested by Gorlin and associates [20]. This is further corroborated by findings following aortic commissurotomy. Although there is still evidence of obstruction, physiologically, patients are relieved of the clinical triad—dyspnea, angina, and syncope—following surgery when the functional valve area is increased to above 1 cm.² [12].

The abnormalities in the brachial artery pressure tracing observed in this series are similar to those reported previously [9]. Estimation of the degree of aortic obstruction could not be made from the contour of the peripheral pulse. This study fails to record any constant relationship between the pressure gradient, stroke output, or valve area and the position of the

notch on the upstroke or time to the peak of systole.

The ability of the ventricle to compensate for the lesion was seen clinically by reviewing the roentgenographic size of the heart. The small hypertrophied left ventricle was capable of

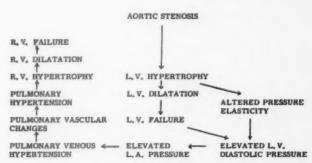


Fig. 6. Schema showing clinicophysiologic events in aortic stenosis. (See text.)

generating higher pressure gradients with larger cardiac outputs than the large dilated hearts (3 plus or greater). As pointed out above, the end diastolic pressure of the left ventricle may be elevated above normal in both instances—in one this is an expression of decreased distensibility secondary to hypertrophy alone, while in the latter it is secondary to myocardial failure.

In summary, aortic stenosis is constantly accompanied by a pressure gradient across the aortic valve. When the obstruction is severe, the blood flow may be below normal in the absence of failure. Estimation of the degree of obstruction requires a knowledge of flow as well as of the pressure gradient. Left ventricular function is greatly altered. The chamber is hypertrophied. This leads to decreased elasticity of the ventricle with elevation of the diastolic pressure. This may occur before left ventricular failure appears clinically. Left atrial function is also altered. Giant "a" waves, observed in the left atrial pressure tracing are probably the result of the increased resistance to left ventricular filling. Pulmonary hypertension may result from left ventricular failure or increased resistance secondary to pulmonary vascular changes. The latter is probably the result of intermittent rises in the pulmonary venous pressure which occurs during exercise and left ventricular failure. (Fig. 6.)

#### SUMMARY

1. Thirty-seven cases of pure aortic stenosis were studied by simultaneous (combined)

catheterization of the left and right sides of the heart.

2. The cardiac output is generally reduced and is a function of the degree of obstruction, pressure gradient, and state of the myocardium.

3. Left ventricular function is greatly altered with elevation in both the systolic and diastolic

pressures, and left ventricular work.

4. Elevation in the end diastolic pressure may be due to heart failure, overt or subclinical, and/or altered pressure-volume elasticity relationships secondary to hypertrophy.

5. A critical valve area (<1.0 cm.2) exists

below which clinical symptoms appear.

6. Estimation of the degree of obstruction requires a knowledge of both aortic pressure gradient and blood flow.

7. No correlation could be made between the contour of the brachial artery pressure tracing

and the degree of obstruction.

8. Combined heart catheterization is not only of value in estimating the degree of obstruction but in evaluating the results of aortic valve surgery.

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# The Phonocardiogram in Mitral Valvular Disease\*

A Correlation of Q-1 and 2-OS Intervals with Findings at Catheterization of the Left Side of the Heart and at Mitral Valvuloplasty

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The selection of patients with mitral stenosis for operation is a common and important medical problem. The use of clinical, electrocardiographic and radiologic methods by a competent cardiologist will lead to a correct decision in most cases. When such consultation is not available, or in problem cases, there is a need for more objective evaluation. The questions to be answered are: (1) how much mechanical mitral valve obstruction actually exists, and (2) is the mitral lesion predominantly stenosis or regurgitation?

Catheterization of the left side of the heart now allows physiologic assessment of the degree of mitral valve obstruction. The evaluation of mitral regurgitation is a more difficult problem. If catheterization of the left side of the heart, however, is combined with a study of indicator dilution curves a more accurate evaluation of the relative importance of the two valve lesions should be possible. Because these technics are arduous and not widely available, there is an important place for simpler methods of answering these questions.

Wells [1], Kelly [2] and others [3-5] drawing upon earlier observations of Weiss [6], Margolies [7], Cossio [8] and Messer [9] have proposed that the phonocardiogram be used to evaluate the degree of mitral stenosis. Two quantitative features of the phonocardiogram in mitral stenosis

are the basis of this evaluation. (1) The time interval between the beginning of the QRS of the electrocardiogram and the first heart sound (Q-1) is prolonged in mitral stenosis, and the degree of prolongation is said to vary directly with the degree of stenosis. (2) The time interval between the second heart sound and the opening snap of the mitral valve (2-OS) is said to vary inversely with the degree of stenosis.

These phonocardiographic features are probably related directly to the hemodynamic abnormality of mitral stenosis. This lesion constitutes an obstruction to diastolic filling of the left ventricle and leads to elevation of left atrial pressure above left ventricular pressure during the diastolic filling period. In other words, mitral stenosis creates a diastolic pressure gradient across the mitral valve, whereas in the absence of mitral valve obstruction these two pressures are virtually identical. The magnitude of the pressure gradient is determined by the degree of narrowing of the mitral orifice and by the rate of blood flow through the mitral valve in diastole. Flow is determined by the cardiac output, heart rate, and duration of the diastolic filling period. It is also affected by mitral regurgitation which increases the forward mitral valve flow in diastole by the amount of blood regurgitated during the previous systolic ejection period.

The Q-1 interval represents the elapsed time

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between the beginning of electrical activation of the ventricle, and the closing of the mitral valve, denoting the beginning of the rise in left ventricular pressure. This interval is normally about 0.04 seconds [10]. Since left atrial and left ventricular pressures are normally identical at the end of the diastolic period, the mitral valve closes as soon as the left ventricular pressure begins to rise or as soon as left ventricular pressure exceeds that in the atrium. The Q-1, therefore, reflects largely the electrical-mechanical interval of the left ventricle. In mitral stenosis, however, with a left atrial pressure appreciably higher than left ventricular pressure at the end of diastole, more time must elapse before the left ventricular pressure can rise to a level sufficient to reverse this gradient. Closure of the mitral valve is delayed for this reason. This is the postulated hemodynamic basis for the prolongation of the Q-1 in mitral stenosis and the basis for its use in assessing the degree of mitral stenosis. It would seem reasonable to expect the degree of prolongation to be proportional to the size of the end diastolic pressure gradient.

Variations in the Q-1 with previous cycle length [9] should be a reflection of variations in the end diastolic pressure gradient with cycle length. Such variation in the end diastolic gradient with cycle length is now known to be a highly characteristic hemodynamic feature in patients with mitral stenosis and atrial

fibrillation.

It is known from studies of catheterization of the left side of the heart that patients with predominant mitral regurgitation and valve sizes in the range of 1.5 to 3.5 sq. cm. often have large pressure gradients across the mitral valve during diastole. Such diastolic pressure gradients result from a mild or moderate degree of stenosis, and a greatly increased blood flow across the mitral valve in diastole, since both the regurgitant flow from the previous cycle and the forward stroke volume flow together into the left ventricle. In patients with pure mitral regurgitation, on the other hand, no measurable diastolic pressure gradient, at least in the mid and late portions of diastole, can be demonstrated. Patients with mitral insufficiency may, then, be separated into two groups: those with a diastolic gradient, and hence some degree of associated stenosis, and those without a gradient. The former should demonstrate variation of Q-1 with cycle length, and the latter should not. Previous studies [2,11] on the value of the Q-1 in differentiating mitral

stenosis and regurgitation should be re-evaluated with this information in mind.

The opening snap of the mitral valve is present in the phonocardiograms of the majority of patients with mitral stenosis [1-3,5,7,12], although it may often be inaudible on auscultation, or difficult to distinguish from a split second sound. The opening snap is believed to represent the forcible opening, under increased pressure, of the thickened mitral leaflets at the beginning of the diastolic filling period. The left atrial pressure is the force that opens the valve. and opening occurs at the instant during isometric relaxation when the left ventricular pressure falls below that of the left atrium. Therefore, the higher the left atrial pressure, the sooner during isometric relaxation will it exceed the falling left ventricular pressure and the sooner will the mitral valve open. In other words, the 2-OS should vary inversely with the left atrial pressure, and more specifically, with the left atrial pressure at the peak of the V wave of the left atrial pulse form. This concept is the basis for the assessment of the degree of mitral stenosis by means of the 2-OS.

Another factor influencing the 2-OS is the arterial blood pressure [3] or, more specifically, the aortic pressure at the moment of aortic valve closure. The 2-OS should vary directly with this incisural level of aortic pressure. This pressure can be determined only by recording a direct aortic pressure tracing. It cannot be determined accurately from the systolic, diastolic, mean or dicrotic pressure in a peripheral artery.

Bayer [3] has found good correlation between the 2-OS interval and the pulmonary wedge pressure obtained from catheterization of the right side of the heart. This is in accord with the foregoing explanation because the "PC" pressure is considered to reflect left atrial pressure.

The reliability and clinical usefulness of these phonocardiographic time relationships have been tested by the present study which compares the Q-1 and 2-OS in patients with mitral valvular disease with data obtained from catheterization of the left side of the heart and at mitral valvuloplasty.

#### MATERIAL AND METHODS

A group of forty-nine patients with mitral valvular disease was selected for study. The criteria for inclusion in this group were (1) availability of a technically satisfactory phonocardiogram (patients with QRS of greater than 0.10 seconds were excluded as this may

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prolong the Q-1 interval) and (2) confirmation of the diagnosis either by catheterization of the left side of the heart (thirty-two cases) or operation (thirty-six cases). Of the seventeen patients in whom the left side of the heart was not catheterized, seven underwent direct left atrial and left ventricular pressure determinations at the time of operation, and in four of these, and one other, the right side of the heart had been catheterized preoperatively. Thus hemodynamic data were available in forty of forty-nine patients.

As indicated in Table I, twenty-six patients had essentially pure mitral stenosis, eleven had various combinations of mitral stenosis and insufficiency and five had essentially pure mitral insufficiency. Seven had hemodynamically significant aortic stenosis in addition to mitral stenosis and one of these (Case 32) had tricuspid stenosis as well. The patients with coexistent aortic stenosis did not appear to behave differently from those with only mitral stenosis.

In twenty-one patients pre and postoperative phonocardiograms were available.

In view of the difficulty in comparing estimates of mitral valve size made by a number of different surgeons, and in view of the limitations of hemodynamic formulas, in the accompanying tables and figures the degree of mitral stenosis has been expressed as severe, moderate or mild. Severe implies a calculated valve area of less than 1.0 sq. cm. or a valve which might just admit the tip of the surgeon's index finger. Moderate implies a calculated valve area in the range of 1.0 to 2.5 sq. cm. or a valve which might admit a whole finger. Mild implies a calculated valve area in the range of 2.5 sq. cm. or larger or a valve which would admit two fingers easily and would be termed "wide open" by the surgeons. There were only three major discrepancies (Cases 12, 15 and 32) between the valve area calculated from catheterization of the left side of the heart and the size of the orifice described at the time of operation. In patients with mitral regurgitation and stenosis the degree of mitral stenosis was taken as that described by the surgeon, since the calculated valve area may be falsely small.

The phonocardiograms were taken with a Sanborn Stetho-cardiette at paper speeds of 25 and 75 mm. per second. The latter speed facilitated measurements to 0.01 seconds. Records were made with the patient in a supine position during mid-expiration with the glottis open. Stethoscopic and logarithmic microphones with a medium bell and diaphragm, respectively, were used in the following positions: (1) aortic area, (2) pulmonic area, (3) fourth intercostal space close to left sternal border, and (4) apex. The opening snap was best demonstrated in the third position with a high frequency filter (logarithmic microphone with a medium diaphragm).

The opening snap has no specific morphologic characteristics and was identified as such largely by its position medial to the apex and its time relationship to the second heart sound, usually 0.06 to 0.16 seconds

later. The second component of a split second sound is usually loudest at the base and follows the first portion 0.01 to 0.06 seconds later whereas a gallop or a third heart sound follows much later (0.16 to 0.24 seconds) and occurs usually at the apex [12,13].

The interval between the Q wave or the beginning of the R wave of the electrocardiogram and the first major deflection of the first heart sound (Q-1) was measured as was the interval between the onset of the second heart sound and the opening snap (2-OS).

For each patient with atrial fibrillation a comparison was made between at least ten Q-1 and 2-OS intervals and the length of the previous cycle as recommended by Messer [9]. These intervals were averaged as well as "corrected" to a heart rate of 75 (R-R 0.8 seconds) in the manner of Wells [1].

Twenty-three patients with heart disease not affecting the mitral valve and without systemic arterial hypertension served as control subjects for the study of the Q-1 interval.

The left side of the heart was catheterized by transdorsal puncture of the left atrium [14] and the left ventricle entered by a small polyethylene catheter introduced through the left atrial needle. More recently the use of two needles has permitted simultaneous recording of left atrial and left ventricular pressure. Cardiac output was measured by the indicator dilution method. Evans blue dye was injected into the left atrium or pulmonary artery, serial blood samples were collected from the brachial artery and the plasma was analysed with a Beckman DU spectrophotometer.

#### RESULTS

Q-1 Interval. The Q-1 interval in the entire group of forty-nine patients with mitral valvular disease ranged from 0.05 to 0.09 seconds (Fig. 1) with a mean of 0.07 seconds (standard deviation  $\pm 0.01$ ). Exclusion of the five patients with predominant regurgitation did not alter the mean values. The interval was significantly longer than the Q-1 in the twenty-three control patients in whom the range was from 0.03 to 0.07 seconds, with an average of 0.05 seconds (standard deviation  $\pm 0.01$ ), but there was considerable overlap of the two groups. There was some tendency for Q-1 intervals longer than 0.06 seconds to be associated with more severe degrees of mitral stenosis. However, four such patients (Cases 4, 21, 25 and 31) with proved severe mitral stenosis had Q-1 intervals of 0.06 seconds or less. One of these (Case 31) had clinical evidence of isolated aortic stenosis confirmed by catheterization of the left side of the heart and digital exploration at transaortic valvulotomy. Although the initial catheterization revealed no significant mitral diastolic

TABLE I SUMMARY OF OBSERVATIONS ON FORTY-NINE PATIENTS WITH MITRAL VALVULAR DISEASE

					Q-1	2-08	(sec.)†	Estimated	d Mitral Va (sq. cm.)	lve Area	Left	Mean		rt Rate	Mitra
Case	Age (yr.), Sex		Group*	(84	ec.)†	3-01	(300.) [	В	efore	After	Atrial Mean Pressure (mm. Hg)	Diastolic Gradient (mm. Hg)	Di	aring	Valve Flow (cc./se
				Pre.	Post.	Pre.	Post.	Cath.	Surg.	Surg.	(		Cath.	Phono.	
								Pure Mitra	al Stenosis						
11 12 13 14 15 16 17 18 19 20 21 22 23 24 25	54, F 47, F 44, F 47, F 47, F 47, F 47, F 48, F 47, F 525, F 526, F 7, F 546, F 7, F 546, F 7, F 547, F 548, M 41, F 46, F 47, M 556, M 556, M	NSR NSR NSR NSR NSR NSR NSR NSR NSR NSR		.06 .08 .06 .06 .07 .08 .07 .08 .09 .07 .07 .07 .07 .06 .06 .06 .08 .07 .07		.10 .08 .12 None .07 .08 .09 .07 .08 .09 .07 .08 .09 .07 .08 .09 .05 .08 .09 .05 .08 .09 .05 .08 .09 .07 .08 .09 .09 .09 .09 .09 .09 .09 .09 .09 .09		1.9 1.0 2.4 1.3 (Rt) 0.9 (Rt)  1.3 1.2 (Rt) 1.4 0.7 0.5 (Rt) 0.8 (Rt) 2.0+ 2.2 1.2  0.9 1.2	1.0 (PM) 0.8 1.3 1.2 0.5 0.9 0.8 1.6 1.0 1.5 0.8 0.8 1.7 0.7 0.5 1.2 0.9 0.4 0.7 1.0 0.8	2.0+ 4.0 2.5 2.0+ 2.5+ 3.0+ 2.5+ 3.0+ 2.4+ 3.0+ 2.5+ 2.5+ 2.5+ 2.5+ 2.5+ 2.5+ 2.5+ 2.5	20 18 3 19 (OP) 21 ("PC") 22 25 (OP) 28 20 25 25 (OP) 20 (OP) 5 13 11	9 5 5 5 (OP)  11 15 (OP) 7 19  14 16 (OP)  0 6 9  9 (OP) 14 9	86 86 84 90 70 71 100  77 105 65  82 95	80 80 70 86 70 78 80 75 68 70 100 80 90 75 75 75 75 75 75 90 90 90 90 90 90 90 90 90 90 90 90 90	247 98 250  200 167 131  138 127  103 242 154
					- 1	1	Mitral	Stenosis and	Aortic Steno	sis	-				
28 4 29 4 30 4 31 5 32 5	58, M 50, F	AF AF AF NSR AF AF	IV IV IV III IV IV	.08 .07 .06 .05 .08 .07	.06	.05 .08 None .09 None .07 .10	None	1.0 0.7 0.9 1.5 1.0 1.6 0.7	1.2 0.7 1.0 1.3 0.9 0.8 0.8	2.8 3.0 2.0 3.0 4.0 2.5 3.0+	38 25 20 13 18 13 16	16 20 10 14 13 3	140 98 68 80 67 67 64	90 88 85 60 95 95 80	181 137 133 244 167 134 100
							Mitra	Stenosis and	d Regurgitation	on					
35   4 36   3 37   2 38   4 49   4 40   2 41   3 12   5 13   4	0, F 9, F 6, F 3, F	AF AF	III III IV IV III III	.07 .06 .06 .07 .06 .08 .07 .07 .07	.06	.07 .10 .10 None .10 .10 .08 None None None	.10 None .12	1.7 2.6 0.7 1.6 1.8 1.2 2.5	0.5 1.0 2.5 1.0 1.0 1.3 1.7	2.2 3.0+ 2.5 2.5 3.0+ 3.0+ 2.2 3.5	18 (OP) 20 21 (OP) 6 25 21 15 27 30	12 6 (OP) 3 12 12 7 13 20	90 120 90  96  60 63 140 125 80	51 80 73 60 80 60 68 72 71 115 88	270 175 107 100 335 194
							Pus	re Mitral R	gurgitation						
6 6 7 3 8 4	2, M 7, M 7, M 9, F	AF AF AF	IV IV	.06		None None None None		4.0 2.5+ 4.0+ 3.0 3.0+	3.0+		11 35 16 22 24	1 0 0 0	69 70 92 90 80	50 70 80 70 80	205

Note: OP = From operative data. "PC" = pulmonary "capillary" pressure from catheterization of the right side of the heart. PM = data from postmortem examination. Operative findings were confirmed at postmortem examination in Cases 2, 27, 33, 47 and 48. Post. = postoperative data. Pre. = preoperative data. Rt = catheterization of the right side of the heart. Cath. = catheterization. Surg. = surgery. AF = auricular fibrillation. NSR = normal sinus rhythm.

\* Harken-Ellis Classification [75].

† Corrected for heart rate of 75.

‡ Converted to NSR following surgery.



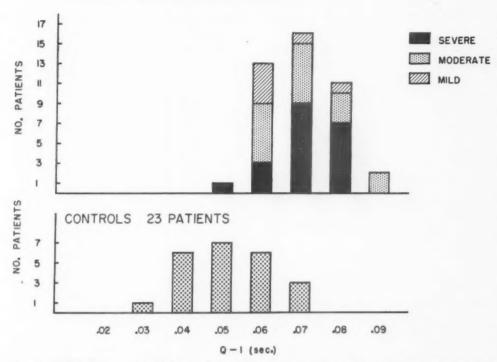


Fig. 1. The frequency distribution of the Q-1 interval in forty-three patients with mitral stenosis of mild, moderate and severe degree, and in twenty-three control patients. Despite the prolonged Q-1 interval in the patients of this study (mean 0.07 seconds) as opposed to the controls (mean 0.05 seconds), the overlap of the two groups permitted no differentiation on this basis.

pressure gradient (in successive but not simultaneous left atrial and left ventricular tracings), at the second postoperative catheterization a mitral diastolic pressure gradient of 13 mm. Hg was found and significant mitral stenosis predicted and confirmed at a second operation. The phonocardiogram had been taken before the first operation and the "normal" findings may have been related to the absence of a measurable gradient at that time.

It is evident, therefore, that the finding of a Q-1 of 0.06 to 0.07 seconds is of very little aid in estimating the degree of mitral stenosis, or indeed in detecting the presence of any mitral valve disease.

There was little correlation between Q-1 and the end diastolic pressure gradient (Fig. 2) across the mitral valve, although most of these gradients were estimated from non-simultaneous tracings and, therefore, subject to significant error. There was also little correlation between Q-1 and left atrial mean pressure (Fig. 3) regardless of the presence or absence of a diastolic pressure gradient. These results fail to support the postulate regarding the genesis of the pro-

longed Q-1 in mitral stenosis. Variations in the electrical-mechanical interval, not measured in this study, might be sufficiently great to obscure small increments in Q-1 caused by the end diastolic pressure gradient which is characteristically present in mitral stenosis. Variations in aortic incisural blood pressure and perhaps some pathological details in individual diseased valves are also uncontrolled variables affecting the Q-1.

In patients with atrial fibrillation, there was an inverse relationship between Q-1 and previous cycle length, as reported by others [9]. According to the hemodynamic postulates presented earlier, this variation should reflect a varying end-diastolic pressure gradient.

Figure 4 shows the relationship of Q-1 to previous cycle length and end-diastolic gradient (measured from simultaneous left atrial and left ventricular pressure tracings) to previous cycle length in the same patient (Case 20). The phonocardiogram and catheterization of the left side of the heart were done at different times but at comparable heart rate and blood pressure. It may be seen from the two graphs that the Q-1 and the end diastolic pressure gradient have the

same relationship to previous cycle length, lending support to the postulate that the degree of Q-1 prolongation depends upon end-diastolic gradient.

Of the five patients with pure mitral regurgitation and atrial fibrillation who were found to tients following mitral valvuloplasty, and in one exceptional case (Case 34) very little had been done to the valve because of marked mitral regurgitation.

2-OS Interval. An opening snap was audible in twenty-two of the forty-nine patients and

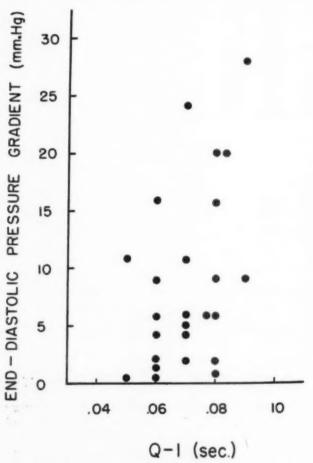


Fig. 2. A comparison of the Q-1 interval in twenty-five patients with mitral stenosis with the end diastolic pressure gradient across the mitral valve determined by catheterization of the left side of the heart. The lack of positive correlation is, in part, due to the fact that the phonocardiogram was taken at a different time, often at a different heart rate and blood pressure.

have no measurable end diastolic pressure gradient, none showed variation of the Q-1 with cycle length and none had Q-1 intervals longer than 0.07 seconds.

However, of the eleven patients (Cases 34 to 44) with combined mitral stenosis and regurgitation and in whom a mitral diastolic pressure gradient was measured, all showed variation of the Q-1 with cycle length and 7 had Q-1 intervals of 0.07 seconds or more.

Postoperative Q-1 Interval. The Q-1 interval became shorter in nineteen of twenty-one pa-

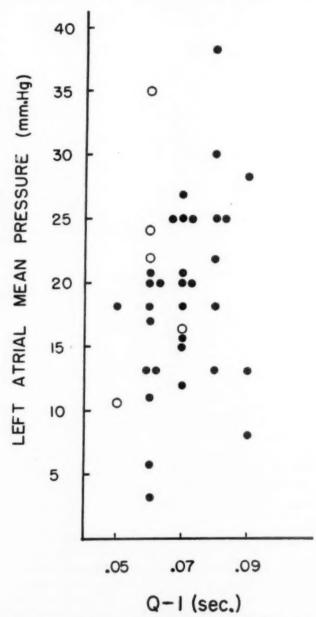


Fig. 3. A comparison of the Q-1 interval with direct left atrial mean pressure in thirty-seven patients with mitral valvular disease. • with gradient,  $\circ$  no gradient.

demonstrable on phonocardiogram in thirtyone. Of the seventeen patients with no demonstrable opening snap, seven had extensive calcification of the mitral valve and virtually no leaflet mobility, and seven had predominant regurgitation or minimal mitral stenosis. The

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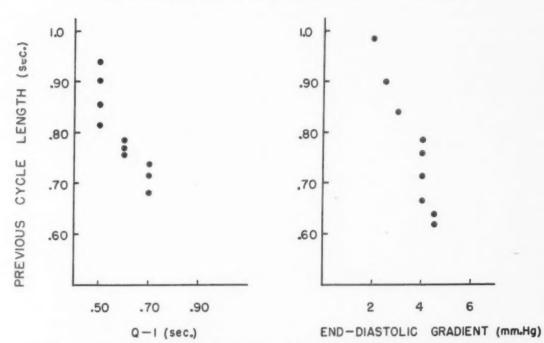


Fig. 4. Case 20, pure mitral stenosis. The variation of Q-1 interval (left) and of end diastolic pressure gradient (right) with previous cycle length. Both the Q-1 interval and end diastolic pressure gradient show an inverse relationship to preceding cardiac cycle length.

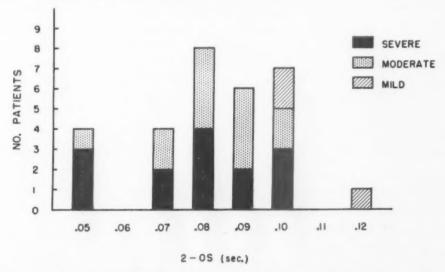


Fig. 5. The frequency distribution of the 2-OS interval in thirty patients with varying degrees of mitral stenosis.

absence of an opening snap is unexplained in the other three patients who had significant mitral stenosis without extensive calcification.

An opening snap was as likely to be present in combinations of mitral stenosis and insufficiency (six of eleven cases) as in pure mitral stenosis (nineteen of twenty-five cases). It was absent in four of five cases of essentially pure mitral regurgitation.

The 2-OS intervals ranged from 0.05 to 0.12 seconds with a mean of 0.08 seconds (standard

deviation  $\pm 0.02$ ). (Fig. 5.) Patients with severe and moderate mitral stenosis showed an almost identical distribution of 2-OS intervals over the range of 0.05 to 0.10 seconds. In three patients with mild stenosis, however, the interval ranged from 0.10 to 0.12 seconds. The presence of a 2-OS interval of 0.09 seconds or shorter indicated moderate or severe mitral stenosis but intervals longer than 0.09 seconds allowed no conclusions regarding the degree of mitral stenosis.

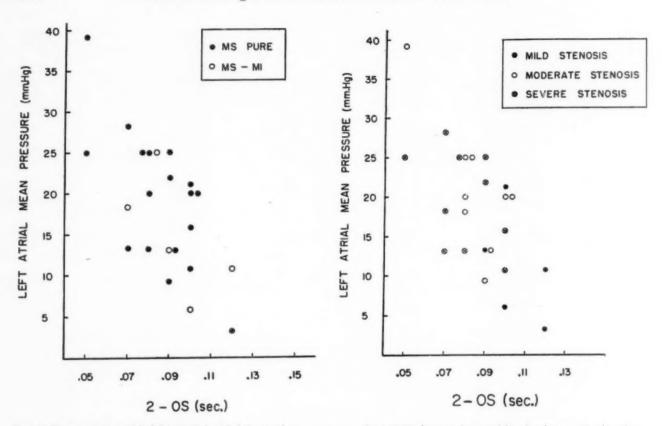


Fig. 6. The variation of 2-OS interval with left atrial mean pressure in twenty-four patients with mitral stenosis, showing inverse correlation (r - 0.7). It is evident that this correlation is independent of the presence of mitral regurgitation (left) or the degree of mitral stenosis (right). MS = mitral stenosis. MI = mitral insufficiency.

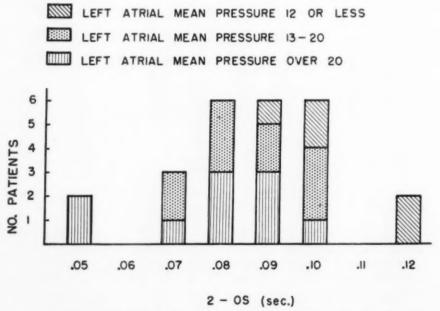


Fig. 7. The frequency distribution of the 2-OS interval in twenty-five patients with mitral valvular disease at varying left atrial mean pressures (mm. Hg).

The 2-OS interval showed significant correlation with left atrial mean pressure (correlation coefficient r = 0.7). (Figs. 6 and 7.) The

variability of the data is such, however, that one can hardly expect to predict the left atrial pressure from the 2-OS with sufficient accuracy

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to be clinically useful unless the interval is very long or very short. The 2-OS interval showed less correlation (r-0.4) with the mean diastolic pressure gradient across the mitral valve (Fig. 8) than with the mean left atrial pressure. These data suggest that the 2-OS interval is determined by the left atrial pressure, independent of the degree of stenosis, or the presence or absence of regurgitation.

Postoperative 2-OS Interval. Following mitral valvuloplasty, the 2-OS interval lengthened in ten of twenty patients, remained the same in four and shortened in one. The opening snap disappeared in four patients and in one patient it became audible and demonstrable by phonocardiogram postoperatively only.

#### COMMENTS

The discrepancies in individual patients between the phonocardiographic intervals and the findings one would anticipate from the theoretical concepts presented herein are not completely explained.

Since the phonocardiograms and the hemodynamic data were not obtained simultaneously, variations in the heart rate, cardiac output and aortic blood pressure may be responsible for some of the differences. Also, failure to recognize opening snaps occurring less than 0.05 seconds after the second sound may influence phonocardiographic interpretation.

Variation in the electrical-mechanical interval from patient to patient may explain the poor correlation observed between Q-1 and the degree of mitral stenosis. The electrical-mechanical interval is technically difficult to measure, and little is known about its variation in clinical conditions.

It is not certain that "correction" of the Q-1 to the standard heart rate of 75 is a satisfactory method of expression. It may be that the uncorrected mean Q-1 interval should be used, or perhaps the longest Q-1 interval observed is the most significant value. Dittrich [4] has mentioned the importance of not only the previous diastolic interval but the two to three consecutive preceding intervals. In other words, the Q-1 interval is longer after three short intervals than it is after only one.

It is quite possible that particular pathologic features of the mitral valve may affect the opening and closing times significantly, as suggested by Wells [1]. The patients who most consistently showed the expected Q-1 and 2-OS deviations

were generally younger women with relatively small hearts and progressive symptoms of recent onset. Such patients are apt to have "tight" mitral stenosis with severe hemodynamic abnormalities, but supple, mobile valve leaflets with the pathology largely limited to fusion

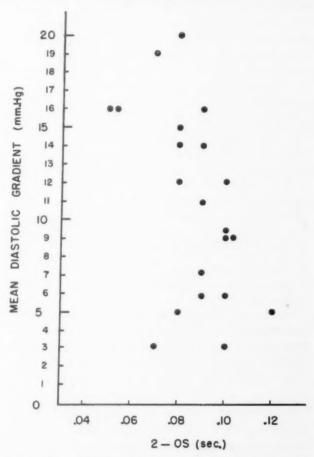


Fig. 8. The variation of 2-OS interval with mean diastolic pressure gradient (r - 0.4) across the mitral valve in twenty-one patients with mitral stenosis.

of the leaflets along the commissures. On the other hand, patients who demonstrated major discrepancies between phonocardiographic data and operative or hemodynamic findings were frequently older, often men, with larger hearts and more chronic disability. Such patients are apt to have more extensive thickening of the valve leaflets, more calcification and more immobility of the valve due to thickening and fusion of the chordae tendineae and papillary muscles.

#### SUMMARY

The intervals between the QRS of the electrocardiogram and the first heart sound (Q-1) and between the second heart sound and the opening snap (2-OS) have been correlated with operative findings and results of catheterization of the left side of the heart in forty-nine patients with mitral valvular disease.

The Q-1 interval was usually prolonged (mean 0.07 seconds, standard deviation 0.01) but there was considerable overlap with the normal range (mean 0.05 seconds, standard deviation 0.02). There was poor correlation of the Q-1 with mitral valve size, left atrial mean pressure or end-diastolic pressure gradient across the mitral valve.

An opening snap was demonstrable in thirty-one patients. Absence of an opening snap was usually associated with a heavily calcified immobile valve, with minimal mitral stenosis, or with the presence of predominant mitral regurgitation. There was significant correlation (r-0.7) between the 2-OS interval and left atrial mean pressure, independent of the mitral valve size. The correlation with the mean diastolic pressure gradient across the mitral valve was considerably less (r-0.4). The left atrial mean pressure or mean diastolic pressure gradient could not be predicted reliably from the 2-OS interval.

Patients with combinations of mitral stenosis and regurgitation and appreciable mitral diastolic pressure gradients, showed Q-1 and 2-OS intervals indistinguishable from patients with pure mitral stenosis and similar pressure gradients. Patients with no diastolic pressure gradients across the mitral valve and, therefore, pure mitral insufficiency, had short Q-1 intervals, usually no opening snap and did not show variation of the Q-1 with the previous cycle length.

With rare exceptions the Q-1 interval shortened and the 2-OS interval lengthened following successful mitral valvuloplasty. Usually the patients in whom this did not occur were not helped by surgery.

It is concluded that the phonocardiogram may be a useful clinical adjunct in the evaluation of mitral valvular disease, but that its usefulness is limited. It is not a substitute for direct hemodynamic studies in patients who present difficult problems.

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### The Effect of Mephentermine Sulfate on Myocardial Oxygen Consumption, Myocardial Efficiency and Peripheral Vascular Resistance\*

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The increasing use of mephentermine sulfate (wyamine®) [1] in a variety of clinical circulatory disturbances [2–6] suggested the desirability of a precise analysis of certain aspects of the pharmacodynamics of this agent. The objectives of this investigation were to ascertain its effects on myocardial contractility, peripheral vascular resistance, myocardial oxygen consumption and myocardial efficiency under controlled experimental conditions. In view of the increased appreciation of the importance of the role of Laplace's law in cardiac energetics [7,8], it was of particular interest to examine the effect of this agent on the oxygen consumption of the heart in various stages of cardiac dilatation.

#### METHOD

Data from four different canine preparations will be presented.

The first preparation was an intact dog anesthetized with morphine, chloralose and urethane, in which observations were made on heart rate and femoral artery pressure.

The second preparation was that which had been devised for the analysis of ventricular function and the effects of drugs thereon; this is described in detail elsewhere [9,10]. Briefly, it consists of an anesthetized dog with an open chest in which cardiac output (minus coronary flow), right and left atrial, pulmonary arterial, and aortic pressures and heart rate are continuously recorded. This will be referred to as the "VF" preparation.

In the third preparation, blood flows from the aorta to a reservoir through an adjustable resistance and flowmeter [11] and is returned to the arterial

system by a pump. The latter has a continuously adjustable rate and stroke volume which are unaffected by changes in peripheral vascular resistance. Left main coronary artery flow [12], in addition to heart rate, cardiac output, left and right atrial, pulmonary arterial, aortic and peripheral arterial pressures are continuously recorded. This preparation will be referred to as the "CF" preparation. In addition to the metering of coronary flow, this preparation has two particular advantages. First, it permits the independent variation and control of aortic pressure, cardiac output and heart rate. Second, peripheral arterial pressure is determined solely by the total peripheral vascular resistance since the pump maintains constant flow into the arterial system; aortic pressure is independently adjusted. This segmentation of the arterial system makes possible a clear differentiation between the effects of any given agent on the heart and total peripheral vascular resistance. Further details of this preparation have been described elsewhere [13].

The fourth preparation was the isolated, supported heart which will be referred to as the "ISH" preparation. It consists of an isolated dog heart in which the blood supplying the myocardium is maintained metabolically normal, or almost so, by continuous exchange with the blood of a donor dog. The details of its preparation, performance characteristics and stability have been described [14]. The main advantages of this preparation, in addition to the completely independent control of hemodynamic parameters, are that it is uninfluenced by reflex neural or humoral factors and that myocardial O<sub>2</sub> consumption is determined with a high degree of precision. It was in this preparation only that the effect of mephentermine on myocardial O<sub>2</sub> consumption was determined.

Work in kilogram meters per minute was calculated

<sup>\*</sup> From the Laboratory of Cardiovascular Physiology, National Heart Institute, Bethesda, Maryland.

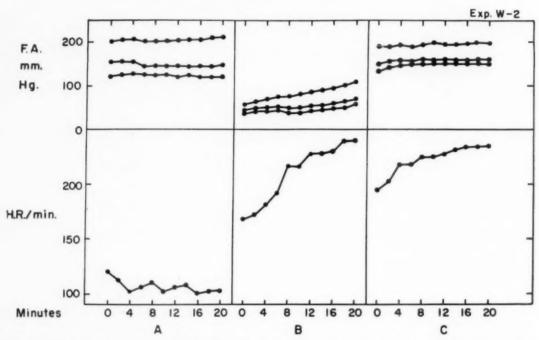


Fig. 1. Effect of ten serial injections of mephentermine, 1 mg. each, at two minute intervals. A = control state, B = three hours later, after induction of hemorrhagic hypotension, and C = three hours after observation B, cervical vagotomy and reinfusion of blood. F.A. = femoral artery pressure. H.R. = heart rate. Experiment W-2. Dog weight = 22.7 kg.

as the product of mean aortic pressure in cm. H<sub>2</sub>O and cardiac output in liters per minute divided by 100. Total peripheral vascular resistance was calculated as the mean aortic pressure in mm. Hg divided by the cardiac output in cc./minute. External efficiency [7] in per cent was calculated as the ratio of work in kilogram meters to the product of O<sub>2</sub> consumption in cc. per minute and 2.06 [15]. The arteriovenous O<sub>2</sub> difference was obtained either by direct gasometric [16] analysis of arterial and completely mixed coronary venous blood or from the continuous recording of arterial and venous densitometers [17,18] which were calibrated in the course of the experiment with five to ten gasometric analyses made in duplicate for each densitometer.

#### RESULTS

The Effect of Mephentermine Sulfate on the Heart Rate in the Anesthetized, Intact Dog. Figure 1 shows the responses to the serial administration of mephentermine under three different circumstances. In A, with the dog's blood pressure and heart rate at control levels, the response to ten doses of 1 mg. each at two minute intervals was bradycardia and minimal arterial pressure changes. In B, three hours later, after hemorrhagic hypotension had been induced, the same course of administration of the drug produced substantial elevations of arterial pressure and a rise in heart rate. In C, three hours after all the

withdrawn blood had been replaced, the original arterial pressure restored, and the vagi sectioned, the same course of administration resulted in a rise in heart rate in contrast to the bradycardia in A when the vagi were intact. These data were representative of three such experiments and were interpreted as suggesting that the bradycardia induced by mephentermine sulfate is reflex in origin and requires an intact vagal pathway. This view is supported by the observation that, when mephentermine is administered to the isolated supported heart (Fig. 5), an increase in heart rate is consistently observed.

Under the same experimental conditions, the use of metaraminol (aramine®), an agent with known constrictor potency [10], resulted in a more striking bradycardia when administered in the control state, as well as during hemorrhagic hypotension. It also resulted in a more striking rise in arterial pressure after vagotomy than did mephentermine.

The Effect of Mephentermine Sulfate on Total Peripheral Vascular Resistance. Figure 2A shows a tracing obtained in a CF preparation in which, following the administration of mephentermine, left atrial pressure fell and heart rate rose, demonstrating the agent's positive inotropic and chronotropic effects. There was, however, only a slight elevation of femoral arterial pressure distal

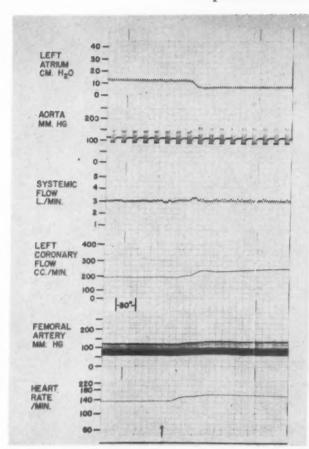


Fig. 2A. C. F. experiment No. 16. Hemodynamic effects of 10 mg. mephentermine injected at time indicated by vertical arrow. Dog weight = 27.3 kg.

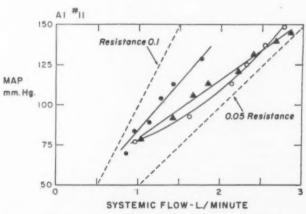


Fig. 3. Pressure-flow relationships in a VF preparation. Control state shown by solid circles, after the administration of 10 mg. mephentermine shown by triangles, and after an additional 30 mg. shown by open circles. Dog weight = 25.0 kg. MAP = mean aortic pressure.

to the pump which maintained a constant flow into the arterial system. In contrast, Figure 2B shows the substantial rise of femoral arterial pressure which occurs after the administration of metaraminol (aramine) under the same

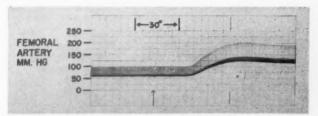


Fig. 2B. C. F. experiment No. 28. The effect on femoral artery pressure of 1.14 mg. metaraminol injected at the time indicated by vertical arrow. Pump output into arterial bed remained constant. Dog weight = 22.7 kg.

experimental conditions. It therefore appears that whereas both agents have a potent influence on the myocardium, as will be shown subsequently for mephentermine and elsewhere demonstrated for metaraminol [10], the former has little influence on total peripheral vascular resistance while the latter substantially increases the peripheral vascular resistance [10].

The effect of mephentermine on peripheral vascular resistance was also studied in the VF preparation with stepwise blood infusion. Figure 3 shows the pressure-flow relationships before, after 10 mg. and after 30 additional mg. of mephentermine sulfate had been administered. These data confirm the observation that this agent has little constrictor effect as determined by calculated total peripheral vascular resistance observations. In this experiment the latter value actually diminished.

Effect of Mephentermine Sulfate on the Left Ventricular Function Curve. It has been shown that the level of aortic pressure at which data for ventricular function curves are obtained influences the height and shape of the curve [19]. In these experiments, therefore, each ventricular function curve was obtained while keeping mean aortic pressure constant, and increasing work by augmenting cardiac output. This was done at each of several different mean aortic pressure levels. The results of a group of such experiments in the ISH preparation are shown in Figure 4A. A striking elevation of the function curves after the administration of mephentermine was observed over the entire range of mean aortic pressures examined. This occurred after the administration of mephentermine, despite the presence of a higher heart rate which is known to lower ventricular function curves [19,20]. Moreover, as shown in Figure 4A, with the higher aortic pressure loads on the left ventricle, the difference between the curves before and after the administration of mephentermine tended to become more pronounced. Figure 4B shows the

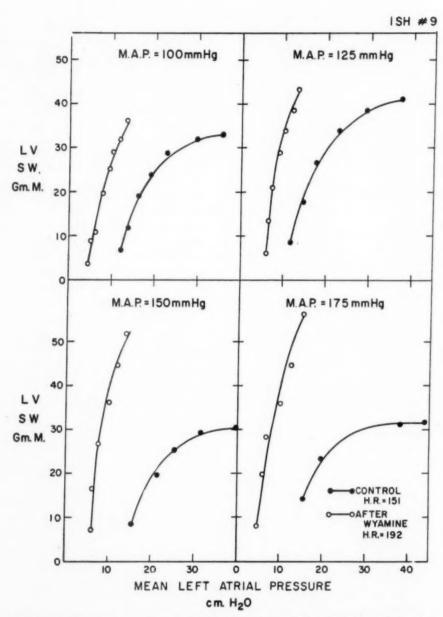


Fig. 4A. ISH experiment No. 9. Four pairs of ventricular function curves obtained by increasing stroke volume at constant mean aortic pressures (M.A.P.), before and after the administration of 10 mg. mephentermine. L.V.S.W. = left ventricular stroke work. H.R. = heart rate. Dog weight = 27.0 kg.

effects of mephentermine on a severely depressed heart in a VF preparation. The administration of 10 mg. elevated the ventricular function curve. An additional 30 mg. produced only a slight further elevation. It was of interest that the further addition of three times the dose that had produced a near maximal elevation of the curve did not either depress the myocardium or produce arrythmias [21–23]. These data are consonant with the results of Goldberg et al. who observed increased contractile force with the strain gage technic after the administration of mephentermine [25].

The Effect of Mephentermine Sulfate on Left and Right Atrial Pressures. As a result of the foregoing it was anticipated that mephentermine would lower atrial pressures, especially when these are initially markedly elevated. It was consistently observed to lower left and right atrial pressures while aortic pressure, cardiac output and ventricular work were either held constant or allowed to rise in the fourteen experiments in which these observations were made. Figure 5 shows the tracing from one such experiment in which the cardiac output aortic pressure and calculated left ventricular work were

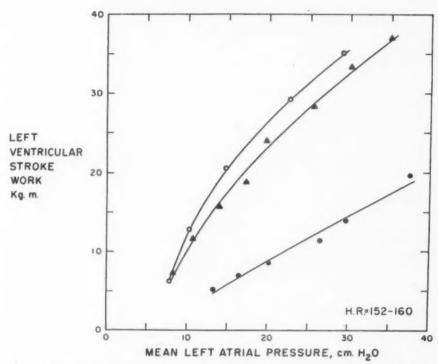


Fig. 4B. Ventricular function curves obtained in a VF preparation. The depressed control curve shown by closed circles; curve after the administration of 10 mg. mephentermine shown by triangles and curve after an additional 30 mg. mephentermine shown by open circles. H.R. = heart rate. Dog weight = 25.0 kg.

permitted to rise after administration of the drug. The left atrial pressure, initially markedly elevated at 44 cm. H<sub>2</sub>O, promptly fell to 6 cm. H<sub>2</sub>O while left ventricular stroke work rose from 31.3 to 42.1 gm. M. and left ventricular work per minute rose from 4.26 to 10.96 kg. M. Right atrial pressure fell from 6.5 to 1.5 cm. H<sub>2</sub>O. The heart rate rose from 136 to 260/minute. Similar results are shown in Figure 6A whether the heart rate was allowed to vary or was held constant.

The Effect of Mephentermine on Myocardial O2 Consumption and External Efficiency. Figure 6A shows the effect of mephentermine on myocardial O2 consumption and external myocardial efficiency in three different isolated hearts when this agent was administered at varying left heart filling pressures. In each instance mean aortic pressure, cardiac output and left ventricular minute work were held constant or almost so before and after the administration of the drug. In the panel on the left (ISH No. 13), the filling pressure was initially 12.3 cm. H<sub>2</sub>O. The drug produced a rise in O2 consumption and a decrease in efficiency, only part of which could be accounted for by the increase in heart rate [7]. In the middle panel (ISH No. 25), when the filling pressure was initially 29.5 cm. H<sub>2</sub>O, little change in O2 consumption and efficiency oc-

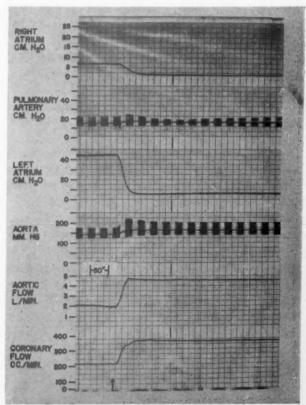


Fig. 5. ISH experiment No. 10, showing hemodynamic effects of 10 mg. mephentermine injected at time indicated by vertical arrow. Heart rate rose from 136 to 260 per minute. Dog weight = 24 kg.

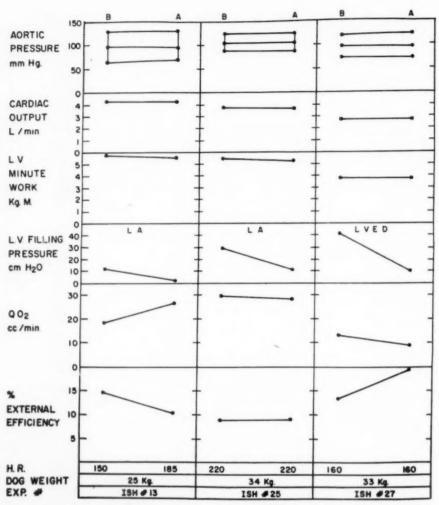


Fig. 6A. Effects of mephentermine on three ISH preparations. B = before mephentermine, A = after mephentermine. L.V. = left ventricle.  $\dot{Q}O_2 = myocardial$  oxygen consumption. H.R. = heart rate. L.A. = mean left atrial pressure. L.V.E.D. = left ventricular end-diastolic pressure.

curred. On the right (ISH No. 27), when the filling pressure was initially 41.4 cm. H<sub>2</sub>O, the drug decreased O<sub>2</sub> consumption by 30.4 per cent and increased external efficiency from 13.5 to 19.5 per cent. It was possible to carry out a more controlled type of experiment by observing the effect on QO<sub>2</sub> of continuous infusions of the shorter-acting nor-epinephrine in one heart at both low and high left ventricular end diastolic pressures. Heart rate, aortic pressure and cardiac output were held constant throughout each infusion. The results were similar to those shown for mephentermine in Figure 6A.

In conjunction with the influence of mephentermine on myocardial QO<sub>2</sub>, an example of its effect on the duration of systole and other hemodynamic parameters is shown in Figure 6B. Left ventricular end diastolic pressure fell from 26 to 12 cm. H<sub>2</sub>O with no significant change in QO<sub>2</sub> (10.6 to 10.4 cc./minute) and no change in external efficiency. Heart rate, cardiac output and mean aortic pressure were held constant. Isometric contraction shortened from 50 to 30 m. second (40 per cent), duration of ventricular systole shortened from 220 to 150 m. second (32 per cent), and the duration of diastole increased from 162 to 232 m. second (43 per cent). The tension-time index per beat (mean systolic pressure times duration of systole) fell from 30.4 to 20.2 mm. Hg seconds. Coronary flow rose from 79 to 97 cc./minute (23 per cent) and the A-V O<sub>2</sub> fell from 13.4 to 10.7 volumes per cent (20 per cent) as the result of a rise in coronary venous oxygen from 6.2 to 9.0 volumes per cent.

The Effect of Mephentermine on the Relationship Between the Ventricular Function Curve and Myocardial O<sub>2</sub> Consumption. Figure 7 shows an ex-

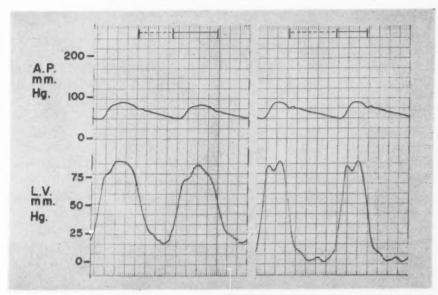


Fig. 6B. ISH experiment No. 28. Effect of 10 mg. mephentermine on duration of systole (solid lines) and duration of diastole (broken lines). A.P = aortic pressure, L.V. = left ventricular pressure. Dog weight = 27.0 kg. See text. Slight pulsus alternans present before mephentermine.

periment in which the ventricular function curve had become depressed and a descending limb had appeared. Six determinations of myocardial QO2 were made, three on the ascending limb and three on the descending limb. Five mg. of mephentermine were then administered and another ventricular function curve obtained by again increasing stroke volume at the same mean aortic pressure and heart rate. Simultaneous OO2 determinations were obtained. The following results were noted: (1) Before the administration of mephentermine, with the left ventricle on its descending limb, as filling pressure was further increased, QO2 continued to rise slightly while external stroke work fell; external efficiency was thereby diminished. (2) After the administration of mephentermine the descending limb did not appear even at the higher work levels, and the divergent relationship between work and OO2 at a constant mean aortic pressure and heart rate was not observed. (3) At comparable left ventricular end diastolic pressures, the external efficiency was higher after the administration of mephentermine. (4) At comparable QO2 levels the filling pressure was lower after the administration of mephentermine

#### COMMENTS

It is clear that the so-called "vasopressor" amines may elevate arterial pressure in different ways but that, as emphasized by Alexander June, 1958

[24], the physiologic mechanisms involved have not always been precisely defined. At any given heart rate arterial pressure may rise as a result of (1) an increase in cardiac output due to an increase in myocardial contractility, (2) an increase in total peripheral vascular resistance or (3) a combination of these effects. For example, methoxamine (vasoxyl®) has relatively little influence on myocardial contractility or may actually depress it [25] but has a powerful peripheral vasoconstrictor effect. Increases in arterial pressure produced with this agent are accompanied by elevations of left atrial and pulmonary capillary pressures which may sometimes be striking [26]. Metaraminol and norepinephrine increase both myocardial contractility [10,25] and total peripheral vascular resistance as shown herein (Fig. 2B) and elsewhere [10]. In contrast, mephentermine exerts its effect primarily on myocardial contractility (Figs. 4-7) with little influence on peripheral arteriolar resistance (Figs. 2A, 3). The data cited are not consonant, therefore, with the previously held view [2-4] that mephentermine produces its therapeutic effect primarily by increasing peripheral vascular resistance. Lastly, the extent to which any given sympathomimetic amine will influence cardiac output and arterial pressure will also depend upon the induced changes in venous tone [27,28]; such information is not yet available for mephentermine.

The significance of the increase in the length

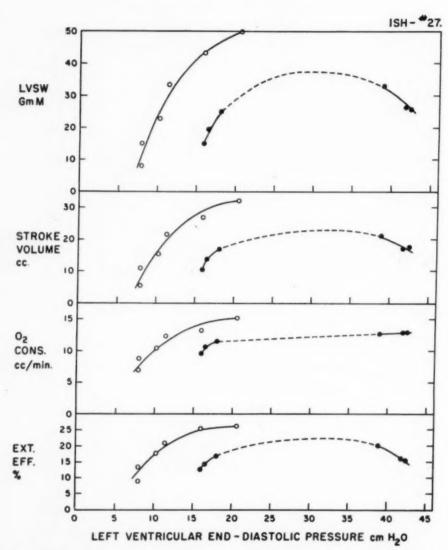


Fig. 7. Relationship between left ventricular end-diastolic pressure and left ventricular stroke work (L.V.S.W.), stroke volume, myocardial oxygen consumption ( $O_2$  cons.), and external efficiency (ext. eff.). Control observations shown by solid circles. Observations, following 5 mg. mephentermine indicated by open circles. ISH experiment No. 27. Dog weight = 23.6 kg.

of diastole, during which the major portion of coronary flow occurs [15], after administration of agents such as mephentermine [35] may be appreciated from Figure 6B. The decrease in systolic duration and consequent prolongation of diastole were accompanied by an increase in coronary flow and a narrowing of the A-V O<sub>2</sub> difference resulting from a rise in coronary venous O<sub>2</sub>. This occurred while there was no change in myocardial O<sub>2</sub> utilization. All other things being equal, the increase in diastole may be of significance when myocardial oxygen availability is limited by coronary artery disease. This may be one of the effects of the agent which helps to explain the reported benefit derived

from its use in patients in whom circulatory failure develops after myocardial infarction [2-4].

At any given heart rate, the increased O<sub>2</sub> requirement of the heart accompanying a given augmentation of cardiac output will be a function of the extent to which any associated increase in peripheral resistance elevates arterial pressure above that level which would occur with the augmented output alone [7]. From the point of view of coronary perfusion, it is obviously desirable to maintain an adequate aortic pressure. On the basis of these considerations it would appear, however, that if coronary perfusion is inadequate because of depressed myo-

cardial contractility, the more desirable means of increasing coronary perfusion pressure is by elevating aortic pressure as a consequence of an augmented cardiac output especially since external myocardial efficiency is increased by the latter [7,13].

Increased O2 utilization and decreased external efficiency, the so-called "oxygen wasting" effect of the sympathomimetic amines, have been the subject of numerous investigations and have recently been discussed by Raab [29]. In most of these investigations adequate experimental control of the pertinent hemodynamic parameters was lacking but the body of evidence does suggest that, in general, this group of compounds increases the O2 utilization of the myocardium. The reasons for this effect are not fully known. The calorigenic effect of these agents provides one possible explanation [30]. Eckstein [31] has suggested that these drugs may cause the ventricle to exhibit a "clenched fist" type of phenomenon; end systolic emptying becomes complete or almost so and the ventricular myocardium continues to develop further tension isometrically and therefore requires additional O2 [7] without further elevation of ventricular pressure or stroke volume, thereby decreasing its efficiency. Another interpretation is that the administration of mephentermine and other sympathomimetic amines results in an increase in the rate of development of the tension of ventricular systole (Fig. 6B) which, of itself, may increase the O<sub>2</sub> requirement [7].

Whatever the explanations of the so-called oxygen wasting effect, the experiments herein described indicate that the administration of a sympathomimetic amine is not necessarily followed by a decrease in external myocardial efficiency. Under circumstances of cardiac dilatation, in the presence of which their use might be appropriate, the administration of such agents may, instead, exert an "oxygen conserving" influence. This view is supported by the data from the three experiments shown in Figure 6A. A decreased external efficiency was observed following the administration of mephentermine when filling pressure was initially 12.3 cm. H<sub>2</sub>O, little change was noted when filling pressure was initially 29.5 cm. H<sub>2</sub>O, and a 44 per cent increase in external efficiency occurred when the pre-mephentermine filling pressure was 41.4 cm. H<sub>2</sub>O. Figure 7 suggests that the increase of external efficiency or the reversal of the oxygen wasting effect of the drug will be most prominent

when it is given in the presence of a descending limb.

It is not meant to suggest that this agent has one particular type of direct metabolic effect when filling pressure is low and another when it is high, with no direct effect somewhere in between. These data do, however, bring into sharper focus two pertinent aspects of the energetics of ventricular contraction. The first is that mephentermine diminishes the product of mean systolic pressure and the duration of systole (tension-time index) because of the substantial shortening of systolic duration, and in this manner it tends to counteract the direct metabolic effect of the agent. (Fig. 6B.) Second, these data are consonant with the applicability to the contracting ventricle of Laplace's law [7,8,32,33] which may be summarized by the following: the larger the integrated systolic ventricular radius, the greater the systolic myocardial wall tension required to produce any given systolic ventricular pressure. Since the development of myocardial wall tension is thought to be a determinant of the heart's O2 requirement [7], a reduction of the integrated systolic radius may well be expected to diminish the O2 utilization for the development of any pressure. Further, intraventricular that physical synergism exists between these factors (ventricular radius and the duration of systole) in the failing heart is suggested by the observation of the low rate of development of tension and the consequent prolongation of systole at the same stroke volume in association with dilatation [34,35]. In summary, while the direct metabolic effect of an agent may be to elevate O<sub>2</sub> consumption consistently, the alteration by the agent of parameters such as the duration of systole, initial filling pressure and the radius, may, under particular circumstances, exert an overriding influence resulting in a net change in the opposite direction.

#### SUMMARY

The sympathomimetic amine, mephentermine sulfate (wyamine) produces a striking elevation of the ventricular function curve in the isolated supported dog heart and in the dog with an open chest with a complete circulation. It appears to have little effect on total peripheral vascular resistance. Under controlled hemodynamic conditions, the administration of the drug was observed to increase myocardial O<sub>2</sub> consumption

and decrease efficiency in the non-dilated heart. When filling pressure was high, however, the agent was observed to decrease the O<sub>2</sub> consumption and increase myocardial efficiency. These data have been interpreted as being consonant with the importance of Laplace's law in the relationship between the total tension developed by the myocardium and its O<sub>2</sub> utilization. The possible role of other hemodynamic parameters such as the duration of systole and the rate of development of ventricular pressure have been considered.

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# The Changes in Concentration of Cholesterol in the Serum of Hypertensive Patients During Antihypertensive Therapy\*

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THE concentrations of total cholesterol in the serums of hypertensive patients have been reported to decrease during the administration of the Kempner rice diet [1-3], hydralazine [4], or pentolinium [5]. The present communication contains data on the concentrations of cholesterol in the serums of patients before and during the administration of reserpine, hydralazine and various ganglionic blocking agents. These data confirm the reports that serum cholesterol concentrations decrease during therapy with hydralazine or with ganglionic blockade. They do not demonstrate a similar decrease during administration of reserpine. A parallelism was apparent, in some patients, between changes in blood pressure and changes in cholesterol concentration. An analysis was made of the correlation between these two changes during treatment with each drug. The correlation between the change in cholesterol concentration and the dosage of hydralazine employed was also analyzed.

#### **METHODS**

The series consisted of twenty-one patients who were hospitalized throughout the study in the wards of the Columbia University Research Service, Goldwater Memorial Hospital. All patients had advanced hypertensive disease with some complication (cerebral, cardiac, renal, or combinations thereof) of sufficient severity to require long-term hospitalization. Blood pressures were measured with a mercury sphygmo-

manometer, with the patient recumbent, at 8:30 a.m. and 1:30 p.m. on three days each week, except during the administration of ganglionic blocking agents, when blood pressures were measured three times daily, seven days a week, with the patient sitting. The disappearance of the Koratkoff sounds was accepted as the indication of the diastolic pressure. The lowest systolic and the lowest diastolic of three determinations were recorded on each occasion. The blood pressures recorded in the tables are the averages of all determinations in the indicated periods. Mean blood pressure is calculated as the diastolic pressure plus one-third of the pulse pressure.

The activity of the patients in the ward was not restricted except as their clinical conditions required. Most patients were on the regular, non-measured, hospital diet. The sodium chloride intake of a few patients was restricted to 3 to 5 gm. per day. No changes in diet were made during any patient's hospital course.

The concentration of cholesterol in the serum was determined by the method of Abell et al. [6]. All determinations were performed in duplicate and results differing by more than 5 per cent were repeated. The shortest pretreatment period was three weeks, the longest twenty-five weeks. All patients accepted for the study had at least three determinations of serum cholesterol concentration during this period. The "control" periods in the tables sometimes include time both before and after treatment. Therapy with each drug was continued for at least four weeks and multiple determinations of cholesterol concentration were made during each treatment period.

There is one exception to this, Table IV.

<sup>\*</sup> From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Columbia Research Service, Goldwater Memorial Hospital, New York City. This study was supported in part by a research grant (H-1397) from the National Heart Institute, National Institutes of Health, United States Public Health Service, and by a grant from the Albert and Mary Lasker Foundation.

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Table 1
SERUM CHOLESTEROL CONCENTRATIONS AND BLOOD PRESSURES IN PATIENTS TREATED WITH RESERPINE

				Contr	roi							Tre	eatmen						
Patient	#	Duration (wk.)	Co	Choleste oncentra (mg. 9	ation	Blo	ood P	ressure	]	Dose	#	Duration (wk.)	Conce	lesterol entration g. %)	Blo	ood P	ressure	Choles- terol (mg, %)	Δ BP Mea
			Mean	S.D.	Range	s	D	Mean	Av.	Range			Mean	Range	, s	D	Mean		
B.	14	8	229	± 15	202-263	196	101	133	5.9	1-8	9	10	205	185-212	143	82	102	-24	-31
R. B.	3	5	256		249-261			142	11	8-16	7	7	253	229-280	184	93	123	- 3	-15
Н. В.	3	10	206		181-223	215	130	158	4.8	1.5-10	3	19	206	194-211	211	114	146	0	-13
N. Bnn.	3	4	233		222-249	215	138	158	18	12-24	8	8	290	275-315	217	112	147	+57	-1
C. E.	18	30	221	± 20	176-260	150	91	111	1.5	.5-10	14	20	213	180-259	146	74	98	-8	-1
R. H.	11	16	266	± 23	239-312	174	97	123	16	2-32	10	14	251	226-279	165	92	116	-15	- '
). J.	5	4	235	± 16	214-262	191	98	129	6.4	2-14	9	11	212	180-259	161	87	112	-23	-1
A. P.	4	5	228		202-258	193	109	137	13	10-16	5	6	212	202-221	176	97	123	-16	-1
St.	8	9	271	$\pm 28$	232-321	228	83	131	13	12-16	10	10	265	241-310	226	.77	127	- 6	
4. W.	2	3	154		150-157		124	152	7.4	4-8	3	4	143	135-150	187	108	134	-11	-18
A. Jo.	5	5	246	±13	226-260	224	122	156	8.1	5-12	7	6	260	239-300			142	+14	-14
Sm.	3	3	280		213-294	220	123	155	10	4-12	6	4	221	191-250	228	106	147	-59	- 1

Note: # = Number of determinations in indicated period

S.D. = Standard deviation

S = Systolic.

D = Diastolic.

Δ Cholesterol = Control mean minus treatment mean.

#### RESULTS

It has been suggested by others that patients with hypertension [2] or coronary atherosclerosis [7] may exhibit greater variations in serum cholesterol concentration than do normal individuals. Hypertension was present in all of the patients of the present series; coronary atherosclerosis was known to be present in some and may have been present in all. The variations in serum cholesterol concentration exhibited by individual hypertensive patients on this service have been large. One patient with mild hypertension was observed for nine months on a constant regimen without medication or change in diet. Forty-one serum cholesterol determinations showed a range from 200-301 mg. per cent and a standard deviation of ±38 mg. per cent. Single determinations in control and treatment periods cannot be used safely to indicate an effect of treatment. An analysis of the change between the first and second cholesterol determinations during the control periods of the twenty-one patients described in this paper showed a mean change of only plus 3.4 mg. per cent. However, individual changes ranged from -80 to +67 mg. per cent.

An evaluation of the trend during the control periods of the seventeen patients who were

admitted to the hospital immediately before the study revealed an average decrease of 5 per cent during this period. There were five patients in whom the difference between the initial and final cholesterol concentrations in the control period was in excess of 10 per cent. One of these rose 19 per cent. The others fell 23 per cent, 14 per cent, 27 per cent and 18 per cent. Although occasional significant changes occurred with hospitalization, there was no consistent effect. The control ranges and standard deviations in Tables I to v demonstrate that wide variations in serum cholesterol concentration often occurred during periods when medication, diet and activity remained constant. Only two patients, L. A. and J. R., showed any significant changes in weight, and these could not be correlated with changes in the concentration of serum cholesterol. Even when means of multiple determinations are compared, a change of less than 10 per cent is not considered meaningful on this service.

Average  $\Delta = -9$ 

The changes in the average serum cholesterol concentrations which occurred during treatment with each of the drugs are recorded in Tables 1 to v. The relationships between concentration of cholesterol, dosage of drug and level of blood pressure will be discussed subsequently.

Effect of reserpine (administered orally) on the

Table II
SERUM CHOLESTEROL CONCENTRATIONS AND BLOOD PRESSURES IN PATIENTS TREATED WITH
HYDRALAZINE

				Cont	rol							Tr	eatmen	t					
Patient	#	Duration (wk.)	Co	holest ncentr (mg. 9	ation	Blo	ood P	ressure		Dose	#	Duration (wk.)	Conce	lesterol intration g. %)	Blo	od F	ressure	Δ Choles- terol (mg. %)	Δ BP Mea
			Mean	S.D.	Range	s	D	Mean	Av.	Range			Mean	Range	s	D	Mean	Cholesterol (mg. %)  -30 -18 -40 +3 -52 -43	
R. B.	3	5	256	± 11	249-261	207	109	142	300	300	6	5	226	219-244	168	86	113	- 30	-29
R. H.	11	16	266	± 23	239-312	174	97	123	497	50-1000	16	21	248	216-268	164	91	115	-18	- 8
D. J.	5	4	235	± 16	214-262	191	98	129	250	250	5	5	195	178-217	160	77	105	-40	-24
W. K.	7	8	232	± 42	168-279	190	102	131	462	200-800	18	11	235	212-257	181	96	124	+ 3	- 7
J. R.	18	25	281	± 25	246-330	205	105	138	267	100-400	16	. 20	229	195-303	144	72	96	-52	- 42
L. S.	13	20	181	± 21	144-208	241	108	152	904	0-1000	13	12	133	114-148	173	82	112	-43	-40
P. I.	7	7	197	± 20	181-227	181	111	134	888	400-1000	28	29	168	139-190	160	97	118	-29	-10

Note: # = Number of determinations in indicated period.

S.D. = Standard deviation.

S = Systolic.

D = Diastolic

Δ Cholesterol = Control mean minus treatment mean.

serum cholesterol concentration and blood pressure:

Table I is divided into a control period and a period of reserpine administration. The mean and range of serum cholesterol concentration and of blood pressure of twelve patients are reported for each period. The average change in mean serum cholesterol between the two periods was -9 mg. per cent. The average change in mean blood pressure was -14 mm. Hg. While the direction of change of serum cholesterol concentration was downward in eight of the twelve patients, only four showed changes which represented a deviation of 10 per cent or more from the mean control value. There was one fall of 20 per cent, two falls of 10 per cent and one rise of 13 per cent. In general, there was a large overlap between the control and treatment

cant fall in the serum cholesterol concentration.

There is often a lag of several weeks between the beginning or ending of reserpine therapy and the appearance or disappearance of physiologic changes induced by the drug. For this reason, comparison of the mean values from periods arbitrarily defined by the dates of drug administration may not always give pertinent information. Inspection of the records of four of the patients in this series suggests that there was a slow increase in cholesterol concentration beginning late in the period of drug administration and continuing for a variable number of weeks

ranges. It is clear that reserpine, in the unusually large doses used, produced no consistent, signifi-

after its discontinuation. This effect, whether fortuitous or meaningful, is obscured by the arbitrary time periods employed for the tabular presentation of the data.

Average  $\Delta =$ 

-28

Effect of hydralazine (administered orally) on serum cholesterol concentration and blood pressure: In seven patients treated with hydralazine (Table II) the average change from mean control to mean treatment concentration of serum cholesterol was -28 mg. per cent. The average change in mean blood pressure was -24 mm. Hg. The decrease in cholesterol concentration exhibited by five of the seven subjects was in excess of 10 per cent of the mean control level. During long-term treatment the trend of values often continued downward.

Effect of reserpine plus hydralazine on serum cholesterol concentration and blood pressure: Table III gives data from seven patients treated with reserpine and hydralazine simultaneously. The average change from the mean serum cholesterol concentrations of the control period to the mean concentrations of the treatment period was -29 mg. per cent. The average decrease in mean blood pressure was 31 mm. Hg. The fall in cholesterol concentration was equal to or in excess of 10 per cent of the control mean in five of the seven cases.\*

<sup>\*</sup> Patient F. L. requires special comment. The control and treatment periods were not really comparable. During the control period this patient was in severe cardiac decompensation, was receiving frequent injections of

TABLE III
PATIENTS TREATED WITH RESERPINE PLUS HYDRALAZINE

				Cont	rol							Tr	eatmen						
Patient		Duration		Choleste oncentr (mg.	ation	Ble	ood P	ressure		Oose av.)		Duration	Conce	lesterol intration g. %)	Blo	ood F	ressure	Δ Choles- terol	A BP Mean
	#	(wk.)	Mean	S.D.	Range	s	D	Mean	Re- ser- pine	Hy- dral- azine	#	(wk.)	Mean	Range	s	D	Mean	(mg. %)	
L. A.	4	18	216	11	201-225	195	93	127	2.3	340	15	20	150	107-184	137	65	89	-66	- 38
R. B.	3	5	256	11	249-261	207	109	142	2.8	244	25	28	247	197-302	162	84	110	- 9	-32
D. J.	5	4	235	16	214-262	191	98	129	1	227	31	32	206	178-242	156	77	103	-29	-26
L. S.	13	20	181	21	144-208	241	108	152	3.8	798	47	60	139	111-243	170	78	109	-42	-43
W. K.	7	8	232	42	168-279	190	102	131	5.5	447	7	11	209	198-233			104	-23	-27
L. Sm.	3	3	280	16	263-294	220	123	155	4	870	9	12	210	176-245	-	95	129	-70	-26
F. L.	11	7	180	24	149-231	168	105	126	1.1	307	15	17	214	147-255	166	71	103	+34	-26

Note: 

Note: 

Number of determinations in indicated period.

S.D. = Number of determine S.D. = Standard deviation.

S = Systolic.
D = Diastolic.

Δ Cholesterol = Control mean minus treatment mean.

TABLE IV
PATIENTS TREATED WITH CHLORISONDAMINE

				Co	ntrol								Т	reatme	nt					
Patient			Dura-		Choleste ncentra (mg. %	ation		-	ood sure	I	Dose		Dura-	Conce	lesterol ntration g. %)	I	Blo	od ure*	Δ Choles- terol	Δ BP Mean
		#	tion (wk.)	Mean	S.D.	Range	s	D	Mean	Av.	Range	#	tion (wk.)	Mean	Range	S	D	Mean	(mg. %)	
L. Sm.	Parenteral	3	3	280	16	263-294	220	123	155	13.8		6	7	179	168-186	180	93	122	-101	-33
P. St.	Oral	8	9	271	28	232-321	228	83	131	146		4	3	188	179-204	182	63	103	- 83	-28
J. L.	Oral Parenteral	4	4	288	27	262-324	225	121	156	266 12.4	4-575 5-15	11 7	10	256 228	220-299 215-244	000		140 133	- 22 - 60	-16 $-23$
L. A.	Oral Parenteral	4	18	216	11	201-225	195	93	127	251 10.3	4-510 3-13	9	10	190 157	164-208 157	188 142		130 101	- 26 - 59	$+3 \\ -26$
J. R.	Oral Parenteral	18	25	281	25	246-330	205	105	138	94	9-375 0-12	11	9	246 225	174-280 218-231		88 81	114 104	- 35 - 56	-24 -34

Note: #

= Number of determinations in indicated period.

S.D. = Standard deviation.

S = Systolic.
D = Diastolic.

Δ Cholesterol = Control mean minus treatment mean.

\* Sitting blood pressure.

The concomitant administration of reserpine did not prevent the response of the cholesterol to

mercuhydrin, and had cystitis. Both the decompensation and the cystitis cleared shortly after antihypertensive treatment was started. The rise in cholesterol concentration may have resulted from the improvement in either or both of these pathologic states. If this patient were omitted from the group, the average change in mean cholesterol would be -40 mg. per cent and in blood pressure would be -32 mm. Hg.

hydralazine administration. The data do not establish that the fall with combined therapy was greater than might have occurred with hydralazine alone.

Effect of ganglionic blockade on serum cholesterol concentration and on blood pressure: Tables IV and V present data on patients treated with chlorisondamine and mecamylamine. Three of the five patients in Table IV received chlorisondamine both orally and parenterally at different times.

				Cont	rol							Tr	eatment	t					
Patient	#	Duration (wk.)	Co	Cholesto incentr (mg. 5	ation		Bloc Press		I	Dose	+	Duration (wk.)	Conce	lesterol ntration g. %)		Bloo Pressi		Δ Choles- terol (mg. %)	Δ BP Mea
		(WL.)	Mean	S.D.	Range	s	D	Mean	Av.	Range		(WK.)	Mean	Range	s	D	Mean		
L. Sm.†	3	3	280	16	263-294	220	123	155	28	7-56	4	5	159	153-164	204	109	141	-121	-14
P. St.	8	9	271	28	232-321	228	83	131	2.5	0-20	6	6	119	85-144			96	-152	-45
B. W.	4	7	228	39	170-252	189	125	146	40	3-61	5	7	198	178-216	162	114	130	- 30	-16
W. Br.	8	5	183	8	172-192	178	124	142	32	0-72	3	4	160	155-165	153	104	120	- 23	-22

Number of determinations in indicated period.

SD

= Standard deviation Systolic.

D

Diastolic

Δ Cholesterol = Control mean minus treatment mean.

\* Sitting blood pressure.

† Mecamylamine plus reserpine.

The data are presented for each course of treatment. Every course was accompanied by a decrease in the mean serum cholesterol concentration in excess of 10 per cent of the control mean. During every course of treatment the range of serum cholesterol concentrations was distinctly different from the range during the control period. The average decrease in mean cholesterol between the control and treatment periods was 55 mg. per cent and the average decrease in mean blood pressure was 23 mm. Hg. Therapy with chlorisondamine (ecolid®) was regularly accompanied by a significant, sustained fall in the serum cholesterol concentration.\* Each of the four patients treated with mecamylamine, Table v, showed a significant fall in serum cholesterol concentration.

The average decrease was 81 mg. per cent. The average decrease in mean blood pressure was 24 mm. Hg. These cholesterol changes are outside the range of variation encountered in the control periods.

pressure and changes in serum cholesterol concentration in response to therapy: During the evaluation of these twenty-one patients it became apparent that, at least in some instances, there was a chronologic parallelism between the changes in

Temporal parallelism between changes in blood

blood pressure and the changes in serum cholesterol concentration. These changes often were independent of the nature and dosage of the antihypertensive agent. Figure 1 (J. L.) presents a case in which such a parallelism was evident during both oral and parenteral therapy with chlorisondamine. While the changes in serum cholesterol lag slightly behind those in blood pressure, the directions of change are repeatedly similar. Figure 2 (L. A.) illustrates a similar correlation occurring during three therapeutic periods with different agents in one patient. In the latter portion of the figure there is a sevenmonth period during which treatment with 0.5 mg. of reserpine daily remained constant but changes in both blood pressure and serum cholesterol concentration occurred.

Figure 3 (C. H.) is a presentation of data accumulated during another study [2]. This hypertensive patient was treated with the rice diet of Kempner. After a period of effective dietary control, during which both the blood pressure and the serum cholesterol concentration decreased, the appearance of an increased amount of sodium in the patient's urine indicated that he was obtaining some other food. Concomitantly both the blood pressure and the serum cholesterol began to rise. The final period, designated "oil," is one in which fat intake was intentionally increased but the diet was continued in other

One patient, (Figure 4, J. R.) was treated with hydralazine during a period when the blood

tients have been observed who exhibited a fall in serum cholesterol concentration when ganglionic blocking agents were added to other antihypertensive drug

\* In addition to the patients presented here, four pa-

regimens.

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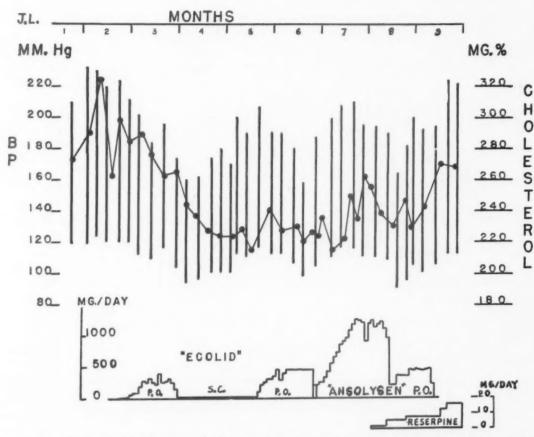


Fig. 1. The changes in blood pressure and serum cholesterol concentration in a patient with essential hypertension, during treatment serially with chlorisondamine, pentolinium and reserpine. Vertical bars are blood pressure averages for one week. Connected dots represent individual determinations of serum cholesterol concentration. P.O. = oral administration. S.C. = subcutaneous administration.

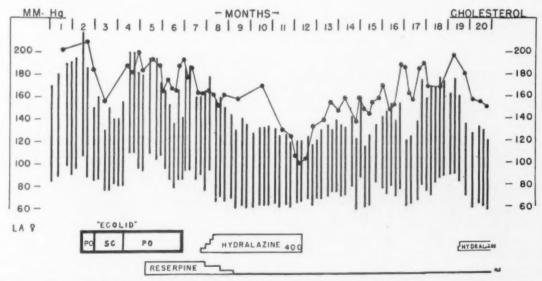


Fig. 2. The changes in blood pressure and serum cholesterol concentration in a woman with essential hypertension, during twenty months of varying antihypertensive therapy. Ecolid = chlorisondamine (P.O. = by mouth, S.C. = subcutaneously). Hydralazine 400 = 400 mg./day in four divided doses. Reserpine maximum dosage was 4 mg./day. Minimum dosage was 0.5 mg./day.

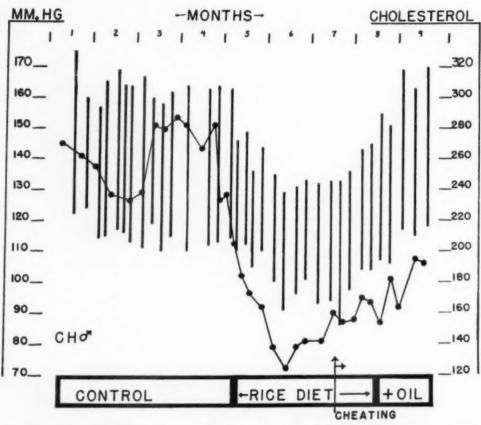


Fig. 3. The changes in blood pressure and serum cholesterol concentration in a man with essential hypertension while eating a normal diet ("control"), the rice diet, and while cheating on the rice diet.

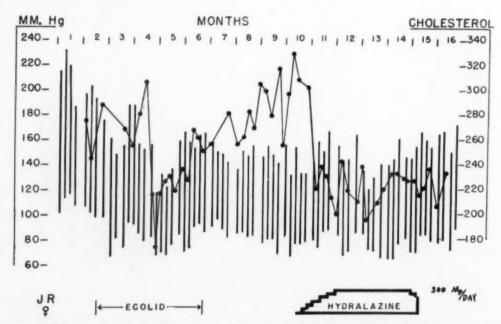


Fig. 4. The changes in blood pressure and serum cholesterol concentration in a woman with essential hypertension, during a period of treatment with chlorisondamine (ecolid), and a period of treatment with hydralazine.

pressure was not very high. No significant change in blood pressure was produced,\* but the fall in serum cholesterol concentration was unequivocal. Prior to this, as illustrated, she had received chlorisondamine when she was

Correlations between changes in serum cholesterol concentration and changes in blood pressure during drug therapy: Figures 5, 6, 7 and 8 show the correlations between the changes in mean blood pressure (in mm. Hg) and the changes in serum

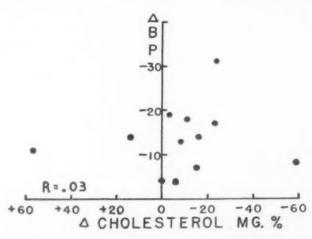


Fig. 5. The correlation between change in blood pressure and change in serum cholesterol concentration of twelve patients during treatment with reserpine. (Table 1.) Each point represents one patient. The ordinate is in mm. Hg and represents the average change in "mean" blood pressure. The abscissa is in mg. per cent and represents the average change in serum cholesterol concentration. No positive correlation is evident.

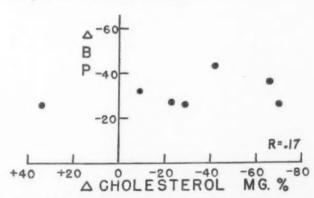


Fig. 7. The correlation between the change in blood pressure and the change in serum cholesterol concentration occurring in seven patients during combined treatment with reserpine and hydralazine. No positive correlation is evident.

hypertensive and both blood pressure and serum cholesterol had decreased.

\* Because this patient was not hypertensive at the time administration of hydralazine was started, her blood pressures were not being determined at the intervals described under "methods." The determinations recorded on the graph are individual determinations instead of week's averages. This patient was also losing weight at a slow, steady rate throughout the entire graphed period, as a result of intentional caloric restriction.

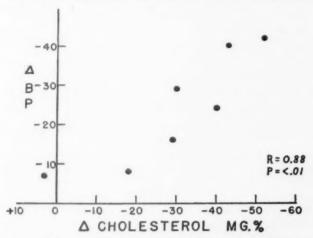


Fig. 6. The correlation between change in blood pressure and change in serum cholesterol concentration of seven patients during treatment with hydralazine.

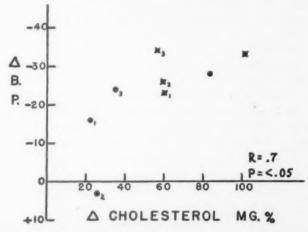


Fig. 8. The correlation between changes in blood pressure and changes in serum cholesterol concentration occurring in five patients during eight courses of treatment with chlorisondamine. Dots = oral administration. Crosses = subcutaneous administration. Like numbers identify two courses in the same patient.

cholesterol concentration (in mg. per cent) during the different types of drug therapy. The data are derived from the tables. Each point represents one patient.\* On the ordinates are plotted the changes in average mean blood pressure in the control and treatment periods. All readings in each period were averaged. On the abscissae

\* Except that in Figure 8, chlorisondamine, the results with oral and parenteral therapy are entered separately as distinct courses of treatment. The two points representing the same patient are identified by the same number.

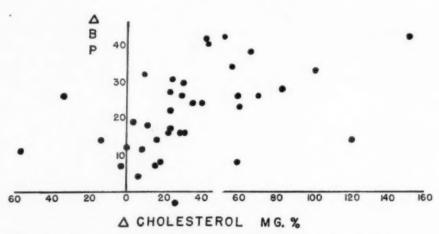


Fig. 9. The correlation between changes in blood pressure and changes in serum cholesterol concentration occurring in twenty-one hypertensive patients, during thirty-eight courses of treatment with antihypertensive drugs. R=0.51, P=<0.01.

are plotted the changes in serum cholesterol concentrations in the control and treatment periods. All measurements in each period were averaged. Therefore, while each point represents only one patient, it represents the averages of many determinations of blood pressure and of

10 00 - 600

Fig. 10. The correlation between hydralazine dosage and change in serum cholesterol concentration occurring in the seven patients represented in Figure 6.

serum cholesterol concentration. The correlation coefficients "R" and, when appropriate, the "P" values are indicated on the graphs. The correlations are neither plotted nor calculated for the mecamylamine group because it included only four patients. Figure 9 presents the combined data from all drug groups, giving a total of thirty-eight courses of treatment. The correlation coefficients is 0.51 with a "P" value < 0.01.

Figure 10 demonstrates the lack of correlation

between the dosage of hydralazine and the change in serum cholesterol concentration produced. A similar plot for the patients treated with chlorisondamine demonstrated a negative correlation.

#### COMMENTS

The data presented in the tables confirm the observations of Perry and Schroeder [4] and of Orvis, Tamagna and Evans [5] that either hydralazine or ganglionic blocking agents are capable of producing a fall in the concentration of cholesterol in the serum. The rice diet may produce a similar change [1-3]. Thus three unrelated forms of treatment of hypertension are each capable of reducing the serum cholesterol concentration. The ability of these three different forms of treatment to lower blood pressure is their only other obvious common attribute.

Two possible explanations have been offered [2,3] for the effect of the rice diet on the serum cholesterol concentration: (1) it is a low fat diet, and (2) it may modify hepatic function. The first explanation is not relevant to the action of either of the classes of drugs. It is possible that hydralazine may modify hepatic function. Morrow, Schroeder and Perry [8] pointed out that therapy with this agent is sometimes accompanied by positive cephalin-cholesterol flocculation tests. Positive cephalin flocculation tests have been common during hydralazine therapy among the patients reported here. The concentrations of bilirubin and alkaline phosphatase in the serums of all of these patients, however, have remained normal, and the serum proteins, as measured by electrophoresis in

paper, have not been discernibly modified nor has retention of bromsulphalein been demonstrable. Needle biopsies of the liver were performed in patients P. I. and L. S. during hydralazine therapy at a time when their serums gave 4-plus cephalin flocculation reactions. A mild degree of bile staining was seen in both sections and slight lymphocytic infiltration was noted in the specimen from P. I. After drug administration had been stopped and the cephalin flocculation test became negative, a second biopsy was normal.

Loyke [9] and Patek [10] have each observed a decrease in arterial blood pressure in association with impaired hepatic function in some patients. This observation, with the suggestions that both the rice diet and hydralazine might be affecting cholesterol concentrations through some alteration in hepatic function, has led one of the present authors (M. E. H.) to favor the concept that the common factor between these forms of treatment may lie in their effect on the liver. To our knowledge, however, no evidence of hepatic damage has been elicited during therapy with ganglionic blocking agents.

Perry and Schroeder [4] have suggested that the effect of hydralazine on the serum cholesterol concentration might be related to the chelating action of this drug, a suggestion which is compatible with the experimental studies of Curran [11]. Such an explanation does not appear relevant to either the rice diet or the ganglionic blocking agents.

The parallelism between changes in blood pressure and changes in serum cholesterol concentration seen in some of the patients described here raises the possibility of a relationship between the two changes. If such a relationship exists it may account for the coincidence that various methods of treating hypertension also affect the serum cholesterol concentration.

A relationship between changes in blood pressure and changes in serum cholesterol concentration in the rat has been demonstrated in this laboratory [12]. It was shown that rats with hypertension develop higher serum cholesterol concentrations on a diet containing added cholesterol, cholic acid and thiouracil, than do normotensive rats on the same diet. No such clear relationship has been shown between blood pressure levels and serum cholesterol concentration in untreated human beings. To date there has been no report comparing multiple determinations of cholesterol in an adequate

number of untreated hypertensive patients with an adequate number of comparable controls which has demonstrated any difference between the cholesterol concentrations of the two groups. It would be helpful if data were available showing whether serum cholesterol concentration is modified when the blood pressure is lowered by sympathectomy or by rigid restriction of dietary salt without restriction of fat or protein intake.

The correlations shown in Figures 6 and 8 are quite compatible with the hypothesis that there may be a relationship between the changes in blood pressure and in serum cholesterol concentration. If the correlation shown in Figure 6 between the changes in blood pressure and cholesterol concentration during hydralazine therapy were to be explained on the basis of two unrelated effects of the same drug then a better correlation than that shown in Figure 10 might have been expected between the dosage of drug given and the change in serum cholesterol concentration produced.

The poor correlations shown in Figures 5 and 7 do not support the hypothesis of a relationship between blood pressure and serum cholesterol concentration. While the comparatively small changes in blood pressure produced by reserpine alone (Fig. 5) might account for the irregularity of serum cholesterol response shown in this graph, it does not account for the poor correlation shown with combined reserpine and hydralazine therapy. (Fig. 7.) The addition of reserpine to hydralazine apparently increased the effect on blood pressure without increasing the effect on serum cholesterol concentration. In addition, in the latter half of Fig. 4, there is a fall in serum cholesterol coincident with hydralazine administration, at a time when no change in blood pressure was demonstrated.

The over-all correlation between changes in blood pressure and changes in serum cholesterol concentration shown in Figure 9 indicates that both functions tend to decrease together during therapy.

#### SUMMARY

1. Data are presented concerning the changes in serum cholesterol concentration and in blood pressure occurring in twenty-one controlled, hospitalized hypertensive patients during treatment with reserpine, hydralazine, reserpine plus hydralazine, chlorisondamine or mecamylamine. There were thirty-eight treatment periods.

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2. The observation of Perry and Schroeder that hydralazine may reduce the concentration of cholesterol in the serum and by Orvis et al. that ganglionic blockade may do the same are confirmed. A similar effect of reserpine therapy could not be established.

3. Possible explanations of the apparent correlation between the changes in blood pressure and in serum cholesterol concentration are discussed. The possibility that there may be a direct relationship between the two functions is suggested.

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## Exaggerated Natriuresis in Essential Hypertension\*

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PATIENTS with essential hypertension excrete more sodium than do normotensive patients in response to the infusion of hypertonic saline solution [1–4]. The work reported in this paper attempts to assay the role of the renal tubule in the genesis of this exaggerated natriuresis.

Our observations confirm the finding that exaggerated natriuresis occurs in hypertensive patients challenged with infusion of hypertonic saline solution, and we find that increased sodium excretion is also induced by infusion of hypotonic inulin and p-aminohippurate solution administered at low rates. However, the basal sodium excretion in hypertensive patients is comparable to that observed in normotensive patients, indicating that both groups are in sodium balance on the same diet; and the exaggerated natriuresis induced in hypertensive patients by infusion of hypertonic saline solution can be abolished by salt deprivation. This and other evidence indicates that the tendency to exaggerated natriuresis in hypertensive patients has an extrarenal basis.

#### **METHODS**

Forty-eight observations on the response to intravenous saline solution were made on thirty-five patients selected from the wards of the Third (New York University) Medical Division of Bellevue Hospital. Essential hypertension‡ (without evidence of circulatory failure) was present in 22 individuals; the remaining 13 were normotensive and free of cardiovascular renal disease. All patients were maintained on the regular hospital diet except for variations in

‡ One patient with advanced hypertensive disease and marked renal functional impairment may have had intrinsic renal disease.

salt intake. Fluids were withheld for 15 hours preceding the test, which was performed in the morning with the patient in a fasting state. Observations were made with the patient supine after a 2 to 3 hour ambulatory period preceding the test. Urine was collected by an indwelling catheter and residual urine was expelled from the bladder by means of air and without washout fluid. In twenty tests urine was collected from the separate kidneys with ureteral catheters; these unilateral observations have been combined for this report. Surgical sterility was maintained throughout the test and an antibiotic (streptomycin or tetracycline) was administered for seventy-two hours following the test.

Control urine samples were collected for the determination of the basal excretion of sodium and water, and of osmolality. After the injection of suitable priming doses of inulin and p-aminohippurate (PAH) [5], a sustaining infusion of these test substances dissolved in distilled water was administered at a rate of 2 ml./minute. Urine was collected during three periods of fifteen to twenty minutes each for the determination of filtration rate, renal plasma flow, osmotic clearance and sodium excretion (U<sub>Na</sub>V). Thereafter an infusion of 2.5 per cent sodium chloride containing inulin and PAH was administered at rates of 12.0 to 13.0 ml./minute for one, two or three hours. Urine collection was continued at twenty- to thirty-minute intervals. Blood was drawn at appropriate times from an antecubital vein into heparinized syringes, centrifuged immediately and the plasma stored in stoppered tubes.

Five normotensive and five hypertensive patients were studied after the dietary addition of 12 gm. of sodium chloride daily for periods varying from four to nineteen days. The response to intravenous hypertonic saline solution was observed in seven hypertensive subjects after salt deprivation: three patients were placed on a rice-fruit diet for ten to fifteen days, two were on self-imposed starvation, and two had

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Table 1

RESPONSE TO HYPERTONIC SALINE INFUSION IN NORMOTENSIVE PATIENTS ON WARD DIET\*

1 Patient	2 Sex	3 Body Surface Area	4 Procedure	5 V (ml./min.)	6  CIN (ml./min.)	7 CPAH (ml./min.)	8 Cosm (ml./min.)	UosmV (mOsm./min.)	UNaV (mEq./min.)	11 NaEF × 100	12 (U <sub>Na</sub> V) U <sub>oam</sub> V × 100
		(sq. m.)								(%)	(%)
F. S.	F	1.70	NI†	1.8			3.4	0.95	0.23		45
			IN†	4.3	103	536	3.4	0.95	0.22	1.4	44
			1 hr.†	1.6	112	742	4.0	1.15	0.41	2.6	44
E. G.	M	1.80	NI	0.92			2.3	0.62	0.11		32
			IN	1.1	135	620	2.6	0.70	0.15	0.8	39
			1 hr.	1.6	213	741	3.5	0.99	0.26	0.9	49
J. K.	F	1.68	NI	0.99			2.4	0.70	0.16		44
			IN	0.97	131	483	2.5	0.73	0.19	1.0	48
			1 hr.	1.5	.138	660	4.0	1.17	0.37	2.1	62
L. G.	F	1.40	NI	0.66			1.4	0.39	0.06		27
			IN	3.2	91	478	1.9	0.53	0.08	0.6	28
			1 hr.	1.3	97	661	2.5	0.71	0.24	1.8	61
M. G.	M	1.52	NI	0.83			2.4	0.64	0.09		25
			IN	2.7	112	619	2.7	0.74	0.07	0.5	18
			1 hr.	0.96	109	676	2.5	0.68	0.15	1.0	37
R. G.	F	1.69	NI	0.47			1.3	0.36	0.02		10
			1 hr.	0.75			2.6	0.72	0.14		35
			2 hr.†	2.6			7.0	1.92	0.71		68
			3 hr.†	5.1			11.3	3.14	1.45		85
U. W.	F	1.45	NI	0.30			0.93	0.26	0.02		12
			1 hr.	3.3	181	934	7.7	2.04	0.68	2.5	62
			2 hr.	9.3	144	735	16.4	4.51	1.98	8.7	81
A. S.	F	1.56	NI	2.2			1.9	0.60	0.07		24
			1 hr.	3.2	131	714	5.9	1.92	0.73	3.7	77
			2 hr.	12.9	138	776	18.2	5.79	2.68	12.8	93
	_		3 hr.	15.6	131	755	21.7	7.00	3.17	16.0	91
K. C.	F	1.32	NI	0.52			1.0	0.29	0.02		14
			1 hr.	0.72	126	662	1.7	0.46	0.10	0.6	42
	_		2 hr.	6.5	132	837	11.1	3.23	1.53	7.2	86
P. H.	F	1.46	NI	3.8	:::		3.5	1.02	0.32		58
			1 hr.	4.8	100	721	9.1	2.54	1.18	8.0	85
1			2 hr.	10.7	108	865	17.6	4.99	2.38	14.6	90
	_		3 hr.	12.3	105	770	19.2	5.59	2.76	16.8	90
A. G.	F	1.74	NI	1.1			2.8	0.78	0.12		29
			1 hr.	1.3	84	522	2.8	0.82	0.20	1.7	46
1			2 hr.	1.6	79	492	3.4	1.00	0.31	2.7	58
			3 hr.	2.8	77	511	5.1	1.53	0.60	5.1	72
R. S.	F	1.61	NI	1.1	407	:::	2.6	0.70	0.18	****	49
			1 hr.	1.1	107	647	2.6	0.68	0.21	1.2	56
			2 hr.	2.1	105	641	4.8	1.27	0.54	3.5	77
		1 11	3 hr.	5.0	111	582	9.5	2.56	1.24	7.3	87
4. F.	F	1.61	NI	1.2	:::	:	2.0	0.58	0.25		81
			IN	1.4	116	554	2.2	0.61	0.21	1.2	53
			1 hr.	1.7	135	744	3.6	0.97	0.34	1.8	65

<sup>\*</sup>Sodium excretion in normotensive patients on ward diet after 1, 2 or 3 hours of infusion with 2.5 per cent NaCl solution at 12 to 13 cc./minute. Columns 5, 6, 7, 8, 9 and 10 are corrected to 1.73 sq. m. body surface area.

† NI = no infusion; IN = inulin and PAH infusion only (2 cc./min.); 1 hr., 2 hr. and 3 hr. = last twenty-minute period of a 1 hr., 2 hr. or 3 hr.

infusion of 2.5 per cent NaCl solution.

been on a salt restricted diet for several months. Observations of basal sodium and water excretion were made in an additional six hypertensive patients.

Inulin was determined by a modification of Harrison's method [6] and PAH by the method of Smith, Finkelstein, Aliminosa, Crawford and Graber [7]. Osmolality of plasma and urine was determined by means of a thermistor bridge-null-point-detector unit [8], using a Johlin freezing point apparatus [9]. The Baird flame photometer was used for sodium determinations.

#### RESULTS

Response to hypertonic saline infusion in patients on ward diet (Tables I, II and Fig. 1): In eighteen

hypertensive patients during the last twenty minutes of a one-hour infusion of 2.5 per cent sodium chloride solution,  $U_{\rm Na}V$  averaged 1.05  $\pm$  0.54 mEq./minute, the sodium excretion fraction NaEF\* averaged 7.7  $\pm$  4.1 per cent, and solute excretion averaged 2.53  $\pm$  1.00 mOsm/minute. In 13 normotensive patients these figures averaged 0.39  $\pm$  0.30 mEq./minute, 2.3  $\pm$  1.9 per cent, and 1.14  $\pm$  0.60 mOsm/minute. Thus sodium and solute excretion

$$fraction (per cent) = \frac{U_{Na}V}{P_{Na}C_{IN}} \times 100.$$

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<sup>\*</sup> Ignoring the Donnan factor, the solution excretion

RESPONSE TO HYPERTONIC SALINE INFUSION IN HYPERTENSIVE PATIENTS ON WARD DIET\*

1	2	3	4	5	6	7	8	9	10	11	12
Patient	Sex	Body Surface Area (sq. m.)	Procedure	V (ml./min.)	CIN (ml./min.)	CPAH (ml./min.)	C <sub>osm</sub> (ml./min.)	UosmV (mOsm./min.)	UNaV (mEq./min.)	NaEF × 100 (%)	(U <sub>Na</sub> V) U <sub>osm</sub> V × 100 (%)
M. F.	F	1.82	NI†	1.1			2.8	0.85	0.09		19
	1	1.02	INT	5.6	128	620	6.5	1.97	0.32	1.9	31
			1 hr. †	7.9		840	11.0	3.21	0.73	3.7	36
D. F.	F	1.53	NI	0.68			2.2	0.61	0.08		27
		-	IN	1.43	101		1.9	0.53	0.07	0.5	26
	_		1 hr.	0.76	105		3.7	1.04	0.34	2.2	59
F. J.	F	1.64	NI	0.28		:::	0.56	0.15	0.02		30
			IN	2.7	95	328	3.0	0.82	0.14	1.0	32
			1 hr.	5.2	120		5.6	1.62	0.50	3.3	57
H. G.	F	1.73	IN	2.9	94	380	3.5	1.01	0.24	1.8	44
			1 hr.	10.0	111	482	10.9	3.20	1.27	7.7	74
R. C.	F	1.43	NI	1.8			3.5	0.98	0.23		43
			IN	3.0	39		5.0	1.38	0.45	8.1	61
			1 hr.	5.0	51		7.4	2.10	0.85	11.8	75
M. H.	M	1.61	NI	2.0			1.7	0.47	0.12		48
			IN	0.95	20	77	1.3	0.37	0.06	2.1	31
	_		1 hr.	9.6	39	158	7.6	2.35	0.89	15.6	71
N. H.	F	1.80	NI	1.0			2.3	0.67	0.12		33
			IN	5.4	81	341	8.5	2.42	1.05	7.7	79
			1 hr.	9.6	165	683	11.7	3.46	1.35	6.2	72
D. B.	F	1.74	IN	0.63	51	201	1.5	0.43	0.12	1.5	49
			1 hr.	7.4	90	387	10.6	3.22	1.52	12.1	. 87
R. D.	F	1.68	NI	0.30			0.64	0.17	0.02		21
		1	IN	6.1	101	394	1.4	0.38	0.08	0.6	40
	-		1 hr.	5.2	145	608	10.0	2.92	1.18	5.6	75
R. L.	F	1.48	NI	0.58		:::	1.4	0.39	0.08		39
1		1	IN	1.6	70	352	2.1	0.60	0.14	1.4	44
	-		1 hr.	2.0	76	476	4.0	1.19	0.36	4.1	56
E. M.	F	1.64	NI	1.2		4774	3.6	1.01	0.12	4.0	22
			IN	0.74	88	471	2.0	0.58	0.13	1.0	41
	-		1 hr.	3.9	96	486	7.3	2.12	0.92	6.4	79
3. G.	F	1.64	NI	1.0	140	424	1.9	0.52	0.10	2.0	38 74
1			1 hr.	4.1	143	424	5.9	1.58	0.64	3.2	
1			2 hr.†	11.3	123	418	14.2	4.01	2.04	10.1	88
		4 50	3 hr.†	20.0	172	669	21.8	6.20	0.10		40
. S.	F	1.52	NI	2.9			2.7	0.74	0.19		48
- 1	_		1 hr.	14.9	89	445	15.7	4.30	2.11	15.9	92
J.	F	1.54	NI	0.47	:::		0.66	0.19	0.03	40.2	25 92
			1 hr.	16.5	144		16.4	4.73	2.42	10.3	
	-		2 hr.	25.9	139		25.6	7.44	3.96	17.5	98
M.	F	1.47	NI	2.5	404	070	2.6	0.75	0.25	4.9	63
			1 hr.	2.7	101	870	6.2	1.66	0.66	4.7	74
			2 hr.	4.1	100	708	8.8	2.51	1.09	8.0	80
	-		3 hr.	7.7	88	708	14.3	4.15	2.02	17.1	89
. G.	F	1.96	NI	0.99	05	674	1.9	0.55	0.14	7.6	49
			1 hr.	5.2	95	674	7.8	2.36	1.07	7.6	83
			2 hr.	12.3	110	693	15.8	4.95	2.38	14.3	86
	-		3 hr.	16.5	126	810	20.9	6.60	3.17	16.2	86
). S.	F	1.57	IN	0.68	44	246	*****	****	0.07	1.2	* *
	- 1		1 hr.	10.6	87	***		0.24	1.19	12.0	
1. S.	F	1.33	NI	0.64		200	1.2	0.34	0.11	4.4	58
			IN	1.2	97	383	2.6	0.71	0.22	1.4	56
			1 hr.	4.0	107	413	6.4	1.86	0.85	6.3	84

\* Sodium excretion in hypertensive patients on ward diet after 1, 2 or 3 hours of infusion with 2.5 per cent NaCl solution at 12 to 13 cc./minute.

Columns 5, 6, 7, 8, 9 and 10 are corrected to 1.73 sq. m. body surface area.

† NI = no infusion; IN = inulin and PAH infusion only (2 cc./min.); 1 hr., 2 hr. and 3 hr. = last 20-minute period of a 1 hr., 2 hr. or 3 hr. infusion of 2.5 per cent NaCl solution.

in response to a challenging infusion are significantly greater in hypertensive than in normotensive patients.\*

In two of the eighteen hypertensive patients U<sub>Na</sub>V did not exceed the average value ob-

\* P value for significance of difference in U<sub>Na</sub>V is < 0.001 and for solute excretion is < 0.001.

served in normotensive patients. In one of these (R. L.) the dietary addition of 12 gm. of sodium chloride daily for four days did not alter the response to the sodium challenge.

Effect of inulin and PAH infusion on sodium excretion (Tables I, II and Fig. 2): The effect of an infusion of inulin and PAH in distilled water, at

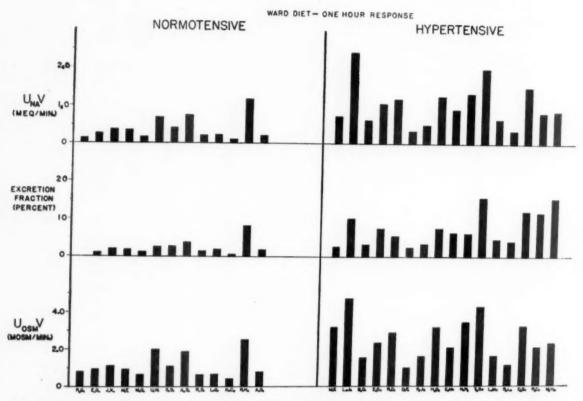


Fig. 1. Response to hypertonic saline infusion. Effect of one-hour infusion of 2.5 per cent sodium chloride on sodium and solute excretion in normotensive and hypertensive patients on ward diet.

a rate of 2 ml./minute, on sodium excretion was observed in sixteen hypertensive and six normal patients. Nine of the sixteen hypertensive patients showed an increase in  $U_{\rm Na}V$ . No increase occurred in the remaining seven hypertensive or in any of the normotensive patients.

Basal U<sub>Na</sub>V on ward diet (Tables I and II): Basal U<sub>Na</sub>V before any experimental procedure other than bladder or ureteral catheterization was comparable in twenty-eight hypertensive and fourteen normotensive patients. U<sub>Na</sub>V in the hypertensive patients averaged 0.12 mEq./minute (range 0.01 to 0.25), while in the normotensive patients this figure averaged 0.12 mEq./minute (range 0.02 to 0.32).

Response of hypertensive patients on low salt intake to infusion of hypertonic saline solution (Table III and Fig. 3): In seven hypertensive patients observed following salt deprivation (less than 200 mg. of sodium daily) for periods ranging from ten days to six months, U<sub>Na</sub>V during the last twenty-minute period of a one-hour infusion of 2.5 per cent sodium chloride ranged from 0.08 to 0.60 mEq./minute. These values may be compared to the range of 0.10 to 1.18 mEq./minute observed in normotensive patients on a ward diet. In three salt-depleted

hypertensive patients (M. B., E. M. and R. D.), prolonging the infusion to two hours re-established the natriuretic response. (Fig. 5.)

Response of hypertensive and normotensive patients on high salt intake to infusion of hypertonic saline solution. (Table IV and Fig. 4): After hypertonic sodium chloride infusion in five normotensive patients on a high salt intake, U<sub>Na</sub>V was greater than in these same patients when on a ward diet. However, in all instances basal U<sub>Na</sub>V after high salt intake exceeded that previously observed in response to infusion while on a ward diet, and the postinfusion value of U<sub>Na</sub>V did not greatly exceed the preinfusion value in four of the five patients.

In only one patient (E. M.) of five hypertensive patients was the peak response to infusion of hypertonic saline solution increased further by high salt intake.

Two- and three-hour response to salt challenge on ward diet (Tables I, II and Fig. 5): Two and a half per cent sodium chloride was infused for two or three hours in seven normotensive and seven hypertensive patients. The peak response in  $U_{Na}V$  in all normotensive patients equalled or exceeded the mean value observed in hypertensive patients at the end of a one-hour infu-

sion. In the seven normotensive patients  $U_{\rm Na}V$  at the end of two or three hours was comparable to that observed in the hypertensive group receiving infusions of similar duration.

Relationship of load to natriuresis (Fig. 6): Comparison of the increment in  $U_{Na}V$  and increment in filtered load,  $P_{Na}C_{IN}$ , showed no correlation in normotensive or hypertensive patients. Furthermore, the increment in  $U_{Na}V$  exceeded the increment in filtered load in 10 of 23 observations in the normotensive group and in 7 of 30 observations in hypertensive patients.

Osmotic excretion and urine osmolal concentration (Tables I, II and Fig. 1): After the infusion of 2.5 per cent sodium chloride for one hour in seventeen hypertensive patients the average solute excretion increased from 0.56 to 2.53 mOsm/minute, as compared to an increase from 0.61 to 1.14 mOsm/minute in thirteen normotensive patients. This increase in solute excretion in both normotensive and hypertensive patients is attributable largely to natriuresis, sodium accounting for 87 to 93 per cent of the increment in solute excretion. Sodium represented 36 per cent of the basal solute excretion in normotensive and 37 per cent in the hypertensive patients. (Tables I and II.)\*

After fluid and food restriction for fifteen hours the osmotic U/P ratio was comparable in eleven of thirteen normotensive and nine of eleven hypertensive patients in whom the filtration rate exceeded 80 ml./minute, this value averaging 2.0 in the hypertensive and 2.2 in the normotensive patients. Two normotensive and two hypertensive patients failed to elaborate a significantly concentrated urine, the osmotic U/P ratio ranging from 0.9 to 1.5.

Renal hemodynamic changes in response to infusion of saline solution (Tables I and II): The filtration rate increased by 4 to 104 per cent (average 42 per cent) in seventeen hypertensive patients and by -3 to 58 per cent (average 16 per cent) in six normotensive patients. Renal plasma flow increased by 3 to 105 per cent (average 49 per cent) in fourteen hypertensive patients and by 9 to 42 per cent (average 30 per cent) in six normotensive patients.

#### COMMENTS

Excessive natriuresis in hypertensive patients has been observed following the infusion of

\* Sodium concentration was converted to osmolal concentration with appropriate activity coefficients, *i*, (International Critical Tables [10]).

hypertonic saline solution [1-4], mannitol [11], 3 to 5 per cent glucose in distilled water, and after the ingestion of water or Swedish Pilsner beer [12]. This increased natriuresis apparently does not depend specifically on sodium, osmotic or water loading because we have induced it

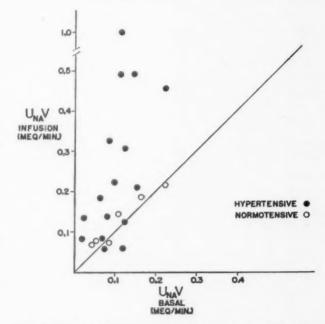


Fig. 2. Effect of infusion of hypotonic solution of inulin and p-aminohippurate in distilled water administered at a rate of 2 ml./minute on sodium excretion in hypertensive (solid circles) and normotensive (open circles) patients. Each datum represents the relation between sodium excretion during infusion and basal sodium excretion in individual patients.

with inulin and PAH in small doses in distilled water infused at a rate of 2 ml./minute (total volume 90 ml.) in hypertensive patients, a response not observed in normotensive patients. In one hypertensive patient (M. H.) U<sub>Na</sub>V increased nine-fold in response to this hypotonic infusion and showed no further increase during hypertonic saline infusion. Farnsworth [13] noted excessive chloride excretion in hypertensive as compared with normotensive patients, an observation confirmed by Weston et al. [14]. Farnsworth attributed the natriuresis (or chloruresis) to a tubular defect in hypertension, but her observations were made during the slow infusion of small quantities of inulin and diodrast® in normal saline solution and possibly represent a natriuretic response to the stimulus of infusion and/or bladder catheterization [15].

In our protocol basal excretion was recorded after catheterization and before any infusion was started, and therefore our basal figures are lower

TABLE III RESPONSE TO HYPERTONIC SALINE INFUSION IN HYPERTENSIVE PATIENTS ON LOW SALT DIET\*

1	2	3	4	5	6	7	8	9	10	11	12
Patient	Sex	Body Surface Area (sq. m.)	Procedure	V (ml./min.)	C <sub>IN</sub> (ml./min.)	CPAH (ml./min.)	C <sub>osm</sub> (ml./min.)	U <sub>osm</sub> V (mOsm./min.)	UNaV (mEq./min.)	NaEF × 100 (%)	(UNaV) UosmV × 100 (%)
E. V. P.	F	1.92	NI† IN†	0.34		389	0.63 0.93	0.18 0.27	0.03 0.05	0.4	28 38
W. K.	M	1.81	1 hr.† NI IN	0.79 0.87 1.0	103	581	2.0 1.2 1.4	0.56 0.35 0.41	0.20 0.06 0.07	1.3	72 31 32
M. S.	F	1.33	1 hr. NI IN	1.4 0.34 0.48	35  46	180	2.0 0.50 0.90	0.59 0.14 0.26	0.14 0.02 0.01	3.1	46 20 10
М. В.	M	1.98	1 hr. NI	4.2 0.18	75	616	3.7 0.60	1.56 0.16	0.60 0.01	7.4	72 10
D.	F	1.95	1 hr. 2 hr.† NI	0.66 4.4 0.32	37 54	261 286	1.8 7.4 0.84	0.49 2.12 0.24	0.08 0.86 0.02	1.4	30 75 12
. M.	F	1.62	1 hr. NI 1 hr.	0.75 0.49 2.8	61	275  606	1.7 0.86 4.2	0.47 0.24 1.13	0.12 0.01 0.48	1.3	45 10 78
. D.	F	1.66	2 hr. NI	7.5 2.3	64	472	9.2	2.62 0.36	1.34 0.04	13.4	95 23
			1 hr. 2 hr. 3 hr.†	0.94 5.8 15.1	87 114 114	548 643 650	1.7 8.8 19.2	0.47 2.63 5.87	0.16 1.20 2.72	1.3 7.2 15.8	63 84 86

<sup>\*</sup>Sodium excretion in hypertensive patients on low salt intake diet after 1, 2 or 3 hours of infusion with 2.5 per cent NaCl solution at 12 to 13 cc./minute. Columns 5, 6, 7, 8, 9 and 10 are corrected to 1.73 sq. m. body surface area.

† NI = no infusion; IN = inulin and PAH infusion only (2 cc./min.); 1 hr., 2 hr. and 3 hr. = last 20-minute period of a 1 hr., 2 hr. or 3 hr.

infusion of 2.5 per cent NaCl solution.

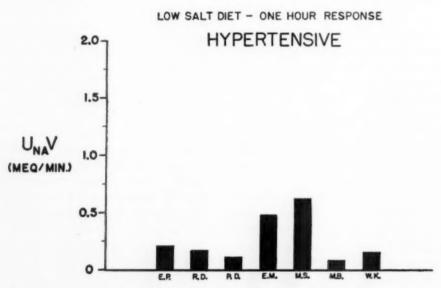


Fig. 3. Hypertonic saline infusion. Effect of salt deprivation on sodium excretion in response to 1 hour infusion of 2.5 per cent sodium chloride in hypertensive patients. To be compared with Figure 1.

than those generally reported by others. The sustaining infusion of inulin and PAH was then started and ninety minutes elapsed between the start of this infusion and the beginning of infusion of hypertonic saline solution (two hours after catheterization); this interval served as a control for the effect of the sustaining infusion and bladder catheterization, and permits us to infer that the later increase in UNaV is attributable to infusion of the hypertonic saline solution.

Our observations confirm those of other investigators, many of whom are cited by Smith [18], showing that in general sodium excretion is not substantially increased in normotensive patients in response to a one-hour infusion of hypertonic or isotonic saline solution. After

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TABLE IV INFUSION IN PATIENTS ON HIGH SALT INTAKE \*

1	2	3	4	5	6	7	8	9	10	11	12
Patient	Sex	Body Surface Area (sq. m.)	Procedure	V (ml./min.)	CIN (ml./min.)	CPAH (ml./min.)	C <sub>osm</sub> (ml./min.)	U <sub>08m</sub> V (mOsm./min.)	UNaV (mEq./min.)	NaEF × 100 (%)	(U <sub>Na</sub> V) U <sub>osm</sub> V × 100 (%)
					No	ormotensive Patr	ients				
M. F.	F	1.61	NI†	2.6			3.9	1.18	0.44		68
M. F.	1	1.01	INT	15.0	133	570	4.9	1.40	0.61	3.4	83
				7.5	133	638	9.5	2.86	1.41	7.2	90
	F	1.40	1 hr.† NI	1.9			3.4	0.95	0.37		69
L. G.	F	1.40			0.5	466		0.88	0.39	2.0	65
			IN	6.4	95	466	3.0				77
			1 hr.	2.3	106	678	4.4	1.26	0.53	3.4	35
M. G.	M	1.52	NI	0.82			2.5	0.70	0.13	0.00	
			IN	0.65	91	498	2.2	0.56	0.10	0.83	35
			1 hr.	1.6	149	709	4.4	1.20	0.33	2.1	48
A. G.	F	1.74	NI	1.3			3.1	0.89	0.30		63
			1 hr.	2.8	108	546	5.6	1.61	0.65	4.1	75
			2 hr.†	8.1	110	472	12.7	3.60	1.71	10.0	87
			3 hr.†	12.7	108	474	17.4	5.14	2.58	15.4	93
R. S.	F	1.61	NI	1.5			3.6	1.01	0.39		71
			1 hr.	1.7	123	511	4.0	1.15	0.48	2.7	76
			2 hr.	3.8	93	450	7.7	2.25	1.07	7.6	87.
			3 hr.	8.8	105	511	14.6	4.36	2.20	14.3	92
					Ну	pertensive Patie	nts		1		
E. P.	F	1.92	NI	1.0			1.7	0.49	0.19		66
A. A.			IN	5.6	104	475	2.4	0.65	0.29	2.0	82
			1 hr.	4.8	119	513	7.9	2.37	1.27	7.3	97
R. L.	F	1.48	NI	1.2	1		2.9	0.81	0.20		45
C. L.	P	1.40	IN	1.6	76	348	3.4	0.92	0.22	2.0	45
			1 hr.	2.3	89	441	4.9	1.43	0.51	3.8	66
- 24	F	1 (4			1			1.16	0.39		60
E. M.	T.	1.64	NI	1.4		415	4.0			5 2	74
			IN	2.3	80	415	5.4	1.56	0.63	5.3	
			1 hr.	7.8	90	487	12.7	3.86	1.83	13.6	84
. G.	F	1.64	NI	1.5	100	204	2.5	0.72	0.20	4.4	52
			IN	1.3	106	304	2.3	0.66	0.21	1.4	60
			1 hr.	3.5	152	388	5.9	1.68	0.71	3.4	78
И. В.	M	1.98	NI	0.95		:::	1.9	0.55	0.14		46
	- 1		IN	0.99	44	191	2.0	0.58	0.15	2.4	47
			1 hr.	4.4	64	284	6.8	2.08	0.87	8.8	77

\*Sodium excretion in normotensive and hypertensive patients on high salt intake diet after 1, 2, or 3 hours of infusion with 2.5 per cent NaCl solution at 12 to 13 cc./minute. Columns 5, 6, 7, 8, 9 and 10 are corrected to 1.73 sq. m. body surface area.

† NI = no infusion; IN = inulin and PAH infusion only (2 cc./min.); 1 hr., 2 hr. and 3 hr. = last twenty-minute period of a 1 hr., 2 hr. or 3 hr. infusion of 2.5 per cent NaCl solution.

#### HIGH SALT DIET - ONE HOUR RESPONSE

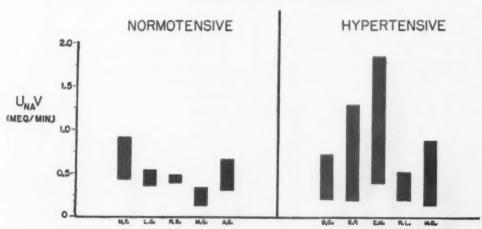


Fig. 4. Hypertonic saline infusion. Effect of high salt intake on sodium excretion in response to one-hour infusion of 2.5 per cent sodium chloride in normotensive and hypertensive patients. Each bar represents the increment in sodium excretion over basal excretion.

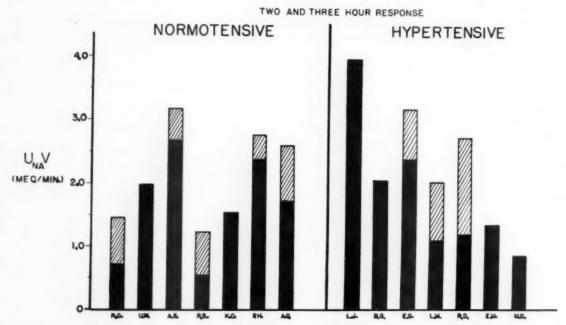


Fig. 5. Response to hypertonic saline infusion. Effect of two- and three-hour infusion of hypertonic saline solution on sodium excretion in hypertensive and normotensive patients. Solid and shaded areas of bar represent sodium excretion at end of two and three hours, respectively. To be compared with Figure 1.

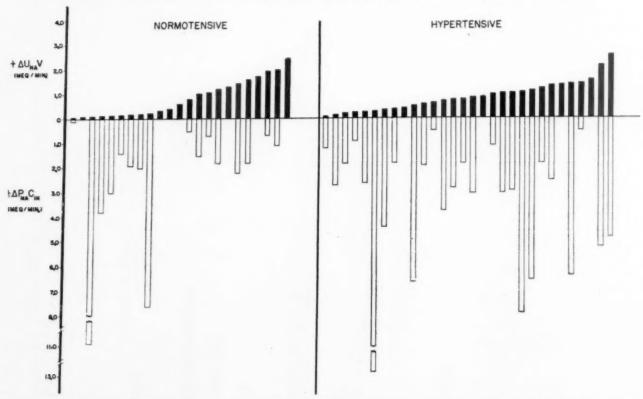


Fig. 6. Relationship of sodium excretion to filtered sodium load. Increment in sodium excretion related to change in filtered load of sodium in all tests (one-, two- and three-hour infusions). The same urine collection period was used to calculate both terms.

infusion for two hours with hypertonic saline solution, however, we find that sodium excretion in normotensive patients assumes the magnitude observed in hypertensive patients. Normotensive patients also respond with exaggerated natriuresis after prehydration with water eight to thir-

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teen hours prior to infusion with isotonic saline solution [16], and after pretreatment with cortisone [2].

Various lines of evidence lead us to conclude that excessive natriuresis following challenging infusions in hypertensive patients is not related to a renal tubular defect. First, sodium excretion under basal conditions and on a ward diet with free access to salt is the same in normotensive and hypertensive patients, and the latter are not salt-losers under ordinary circumstances but remain in balance on the same intake. \* Second, our present demonstration of low sodium excretion in hypertensive patients during salt deprivation indicates that the renal tubule in the hypertensive kidney can conserve salt effectively, a conclusion supported by the fact that hypertensive patients can tolerate prolonged sodium dietary restriction, even when the filtration rate is markedly reduced. Third, exaggerated natriuresis can be abolished in hypertensive patients, regardless of reduction in filtration rate (Table III), by salt deprivation, a result not to be anticipated in the presence of a basic tubular defect.

Since tubular reabsorption of sodium thus appears to be unimpaired in hypertension, the natriuresis which occurs in response to various stimuli and which can be induced in normotensive subjects under circumstances herein described would seem to be initiated extrarenally. Natriuresis occurs with isotonic, hypotonic or hypertonic expansion of the body fluids, with or without sodium chloride as the osmotic load, and with oral as well as intravenous loading. Recognizing that bladder catheterization represents a sensory type of stimulus, it is possible that the slow infusion of small volumes (90 ml.) of inulin and PAH in distilled water may fall in this category. Nevertheless, the data indicate that larger infusions induce additional natriuresis, possibly by expansion of body fluid, but if such is the case we are unable to differentiate between intra- or extravascular and intracellular expansion. As would be anticipated if body fluid expansion is involved, prolonging the infusion to two hours in the salt depleted hypertensive patient re-establishes the natriuretic response.

Normotensive and hypertensive patients elaborated urines of comparable osmotic U/P ratios

\* Urine collections were taken between 8 and 9 A.M. for thirty-minute periods and probably do not reflect twenty-four hour excretion because of the duirnal cyrle.

after fifteen hours of fluid and food deprivation. Since the average ratio obtained in the normotensive patients was less than the expected value of 3 to 4 [17], it is presumed that the conditions of examination were not conducive to maximal antidiuresis. Our data, therefore, do not permit us to conclude that the concentrating mechanism is normal in early hypertensive disease. The failure of two normotensive and two hypertensive subjects, however, to elaborate urine of significant osmotic concentration (osmotic U/P ratio = 0.9, 0.9, 1.0, 1.5) may reflect moderate (water) diuresis resulting from surreptitious water ingestion prior to experimental observation, assumption of the supine position [18], bladder catheterization [15], or a true renal defect in concentrating ability. We cannot choose among these possibilities.

The possibility exists that the increase in filtration rate which is generally observed in hypertension in response to infusion may explain the exaggerated natriuresis. It is recognized that a small increase in filtration rate may be causally related to a significant increase in sodium excretion when the latter is initially small. Our data, however, indicate that the increment in filtered load during infusion does not account for the increase in excretion in about one-fourth (seven of thirty) of the observations on hypertensive patients, and the group as a whole showed no relationship between increased load and increased excretion. Our data suggest that changes in filtered sodium may not have a causal relationship to the exaggerated natriuresis.

#### CONCLUSIONS

- 1. Exaggerated natriuresis can be induced in hypertensive but not in normotensive patients on a ward diet by the infusion of hypertonic (2.5 per cent) saline solution for one hour.
- 2. Increased sodium excretion in hypertensive patients can also be induced without sodium, osmotic or water loading by hypotonic infusion of inulin and p-aminohippurate at a rate of 2 ml./minute (total volume of 90 ml.).
- 3. A natriuretic response comparable to that described in [1], can be induced in normotensive patients by prolonging the infusion of hypertonic saline solution to two hours.
- 4. Maintenance of sodium balance and effective sodium conservation, and abolition of exaggerated natriuresis during salt deprivation in hypertensive patients, indicate that tubular

reabsorption of sodium is unimpaired early in hypertensive disease, and that the exaggerated natriuresis induced in such patients by various stimuli involves an extrarenal mechanism.

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# Carcinoid Syndrome Produced by Metastasizing Bronchial Adenoma\*

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During the past five years the carcinoid syndrome has become an accepted entity. Following the initial impetus given to recognition of this syndrome by Thorson and Biörck and associates [1,2] in 1952 and 1954, based upon the earlier studies by Lembeck [3] and by Erspamer and Asero [4,5], there was enhanced interest in the chemistry and physiology of 5-hydroxytryptamine [6–8], the pharmacodynamic substance produced by metastatic intestinal carcinoid tumors. This substance (serotonin, enteramine) has been recognized as a product of the chromaffin cells of the gastrointestinal tract, the same cells from which the intestinal carcinoid tumor arises.

The following cases of functioning carcinoid tumor are reported not only because their clinical and chemical manifestations are of interest, but also because the primary tumor in each case apparently arose in the lung rather than in the gastrointestinal tract. The possibility of production of the functioning carcinoid syndrome by metastatic bronchial adenoma, carcinoid type, has been suspected by a few observers interested in this field. Although to the authors' knowledge there has been no published report of such a case, there are on file in the Armed Forces Institute of Pathology two equivocal cases of malignant bronchial adenoma, carcinoid type, associated with what appeared to be the functioning carcinoid syndrome [9].

# CASE REPORTS

CASE I. A. M., a forty-eight year old white woman, was hospitalized at the 3575th U.S.A.F. Hospital, Vance AFB, on March 31, 1955, complaining of a recurrent skin eruption during the preceding eleven months and recurrent diarrhea of four months' duration. Nausea and vomiting accompanied the diarrhea. In May 1954, eleven months prior to her hospitalization, she noted the onset of tender peri-

orbital swelling with red discoloration of the face. There was also tender swelling of the soft tissues of the entire face and neck, a red papular rash over the body, and slight swelling of the hands. The skin, particularly on the face, "burned like fire." After its initial appearance, this exanthem recurred periodically usually, at monthly intervals, lasting from four to six days and most often just prior to menstrual periods. The patient's intermittent episodes of diarrhea consisted of nine to twenty watery stools per day accompanied by abdominal cramping and striking borborygmi. These episodes usually occurred in association with exacerbations of the skin eruption. During these episodes she also noted prolonged paroxysms of severe dyspnea and wheezing. From May 1954 to the time of her hospitalization eleven months later, she noted a diminution in the duration and amount of her menstrual flow. Periods occurred only once every

Interrogation as to family history disclosed the fact that the patient's twenty-seven year old daughter was hospitalized with a diagnosis of schizophrenia. The patient's past history revealed that in October 1949, five years prior to this first U.S.A.F. Hospital admission, she had undergone a left pneumonectomy at a private civilian hospital for removal of a tumor in the lung. At the time of this first U.S.A.F. Hospital admission the previous records of the pneumonectomy were not available. According to her own statement, except for slightly increased fatigue and mild dyspnea on exertion, she felt well following the pneumonectomy.

Physical examination at the time of admission to the 3575th U.S.A.F. Hospital disclosed a fairly well nourished, well developed white woman of middle age, in acute distress. The patient weighed 120 pounds. Oral temperature was 99.2°F. The radial pulse was regular at a rate of 122. The blood pressure was 126/80 mm. Hg. The patient's face appeared red and swollen, and her neck presented the appearance of a diffuse brawny type of edema. Increased lacrimation was present. A well healed left thoracotomy scar was noted, and a portion of the fifth rib on the left was absent. The nipples were swollen and red. Breath sounds were absent in the left hemithorax and the percussion note was dull in

<sup>\*</sup> From the 3750th U.S.A.F. Hospital, Sheppard Air Force Base, Wichita Falls, Texas, and the Department of Medicine, The Mount Sinai Hospital, New York, New York.

this area. The right hemithorax showed somewhat increased resonance to percussion but the breath sounds were normal. No cardiac murmurs were noted. The liver edge was felt 5 fingerbreadths below the right costal margin and was tender. There was slight swelling and redness of the fingers of both hands. Red macular lesions were scattered over the skin of the chest and abdomen.

Urine analysis revealed the following: specific gravity 1.011, 2+ proteinuria, and 3 to 4 leukocytes per high power field. No Bence-Jones protein was found in the urine. Studies of the blood yielded the following values: Leukocytes 13,900 per cu. mm. with a normal differential count, hemoglobin 15.3 gm. per cent, erythrocyte sedimentation rate 14 mm. (Wintrobe), total proteins 6.1 gm. per cent, albumin 4.2 gm. per cent, and globulin 1.9 gm. per cent. The serum total bilirubin was 1.1 mg. per cent, and the total cholesterol was 192 mg. per cent. Analysis of a specimen of the gastric aspirate, obtained in the fasting state, disclosed a total acid of 17 degrees. No free acid was present. After histamine stimulation, the maximum total acid was 65 degrees, and 30 degrees of free HCl were found to be present. Roentgen studies of the gastrointestinal tract from the mouth to the rectum disclosed no intrinsic abnormalities. X-ray examination of the chest showed resection of the posterior portion of the left fifth rib, and evidence of marked pleural thickening obscuring the left lung field.

After three days of bedrest and supportive treatment, the patient's skin manifestations, diarrhea and abdominal pain improved. She remained essentially asymptomatic for another three days and then the same symptoms recurred. They lasted for one week and then again spontaneously subsided. At that time intravenous pyelography was carried out in search of renal disease suggested by the finding of 2+ proteinuria. An abnormality involving the collecting system of the right kidney was noted. Since further investigation and diagnostic procedures were therefore indicated, on April 29, 1955 the patient was transferred to the 3750th U.S.A.F. Hospital, Sheppard AFB, Texas. At the time of her arrival a detailed report of her previous thoracotomy and of the illness prompting this operation was obtained and is summarized as

In 1947 the patient first experienced pleuritic pain on the left side of the chest, with non-productive cough and fever, lasting two weeks. In 1948 she had had a similar episode and in 1949 she experienced her third episode of left-sided pleuritic pain. During this latter attack in October 1949 she was hospitalized. Physical examination at that time is reported to have revealed splinting of the left hemithorax, dullness to percussion over the left hemithorax, and the presence of râles in this area. Roentgenogram of the chest was reported as showing a diffuse haziness of the upper half of the lung field and on a lateral view a mass was seen adjacent to the superior portion of the left hilus.

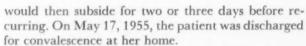
Tumor of the left upper lobe, with some degree of atelectasis of that lobe, was suspected. Bronchography disclosed obstruction of the left upper bronchus. On October 25, 1949, a left pneumonectomy had been performed. Examination of the resected specimen disclosed the left upper lobe bronchus to contain a polypoid plug of dark grey-brown tumor tissue which on cross section extended through the wall of the bronchus into an ovoid mass of grey gelatinous tissue of irregular shape. Many large rounded masses of similar tumor tissue were present throughout the parenchyma of the left upper lobe. The pleura appeared to be involved in some areas also. Numerous small foci of acute pneumonia were present and in some places approached abscess formation. Hilar lymph nodes were not involved. The microscopic diagnoses of the tumor was "carcinoma of the lung." The patient's immediate postoperative course was fairly uneventful and she was discharged from the hospital on Movember 4, 1949.

At the time of her first admission to the 3750th U.S.A.F. Hospital in April 1955, the patient was observed to have a diffuse swelling and erythematous flush of her face. The blood pressure and temperature were normal. The liver edge was palpated 6 fingerbreadths below the right costal margin. It was moderately tender and over its surface numerous nodules of various sizes were felt. Bowel sounds were distinctly hyperactive. The lung findings that were previously noted were found unchanged. Studies of the blood disclosed the following: hemoglobin 11.0 gm. per cent, red blood cells, 3,600,000 per cu. mm., leukocytes 6,100 per cu. mm. with a normal differential count. The serum alkaline phosphatase was elevated slightly to 8.8 Bodansky units. A roentgen study of the colon and terminal ileum disclosed no abnormal findings. An intravenous pyelogram and left retrograde pyelogram disclosed normal findings. Right retrograde pyelogram suggested some degree of obstruction of the right calvceal system. Roentgenogram of the chest disclosed elevation of the left leaf of the diaphragm, absence of lung markings on the left and a moderate shift to the left of the heart and mediastinum. A portion of the left fifth rib was noted to have been resected. A moderate degree of compensatory emphysema was present on the right side. Electrocardiogram disclosed entirely normal findings.

Needle biopsy of the liver was performed. Microscopic examination of the specimen obtained yielded a diagnosis of malignant carcinoid tumor. (Figs. 1 and 2.) The entire biopsy specimen consisted of tumor tissue. Stains for argentaffine granules were negative. Subsequent to the liver biopsy, the patient's course in the hospital consisted of continued intermittent attacks of nausea and vomiting, diarrhea, brilliant red flushing of the face and neck and to a lesser degree of the body, increased lacrimation, dyspnea, profuse sweating and abdominal cramps. Each attack usually lasted from two to five days and



Fig. 1. Specimen obtained by needle biopsy of the liver, consisting entirely of metastatic carcinoid tumor. Hematoxylin and eosin stain, original magnification × 115.



On June 21, 1955, she was readmitted to the 3575th U.S.A.F. Hospital, Vance AFB, because of the recurrence of all symptoms. At the time of that hospitalization the blood pressure was 118/68 mm. Hg, the pulse was 132, and the oral temperature was 99°F. She appeared both acutely and chronically ill, but was alert and cooperative. No cardiac murmurs were noted. The liver was enlarged 7 fingerbreadths below the right costal margin. Bowel sounds were markedly increased. There was a generalized erythematous swelling of the face and neck, particularly of the eyelids and lips; and scattered over the trunk there were reddish papular lesions which blanched easily on pressure. The nipples were reddened and tender. Another barium enema study disclosed no abnormalities in the colon or terminal ileum. Proteinuria persisted.

Hydration and electrolyte balance were maintained by intravenous therapy. In addition, the patient was given chlorpromazine, codeine, meperidine, atropine and antihistamines. A sigmoidoscopic examination disclosed normal findings except for the presence of internal hemorrhoids. After the initial week of bedrest and parenteral alimentation, the patient's symptoms subsided to a degree sufficient to consider allowing her return home. However, two days later all of

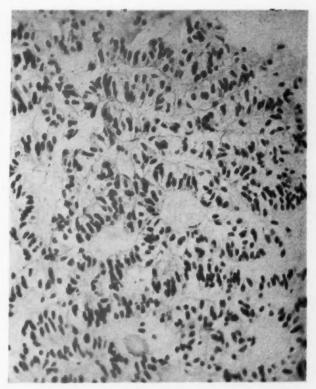


Fig. 2. Liver biopsy specimen seen at higher magnification, demonstrating the cellular characteristics of this malignant carcinoid tumor. Hematoxylin and eosin stain, original magnification × 300.

her previous symptoms recurred, she became irrational and appeared critically ill. She was then transferred for her final hospitalization to the 3750th U.S.A.F. Hospital, Sheppard AFB, where she arrived on July 21, 1955.

Upon admission, the patient was emaciated and appeared both acutely and chronically ill. Temperature, pulse and blood pressure were normal. The respirations were 24 per minute. Her face was swollen and fiery red, and a generalized bright red maculopapular eruption was present over her body. It had previously been noted that one to two or even three days prior to subsidence of an attack her bright red rash usually changed to a maculopapular eruption which, just prior to remission, would become a very discrete red papular eruption with normal-appearing skin between the papules. Filling most of the right side of the abdomen and extending over into the left upper quadrant was a large, lumpy, and moderately tender liver mass. The remainder of the physical findings were not significantly changed from those noted during her previous admission at the Vance AFB Hospital. Laboratory studies disclosed no significant changes in the blood findings. Urine analysis disclosed no abnormalities. Electrocardiogram showed non-specific T-wave changes without any other abnormalities.

During the first three days in the hospital the pa-

tient's rash and general condition improved. However, on July 25, four days after admission, another attack began, with marked dyspnea as the first symptom. Blood pressure fell to 96/50 mm. Hg and shock appeared imminent. She was placed in an oxygen tent and given intravenous levarterenol. She showed no signs of improvement, and on July 28, appeared to be moribund. Coarse rales were heard throughout the right lung. The abdomen was distended and frequent large watery stools were noted. The urine output was reduced to 600 cc. over a twenty-four hour period. However, that night there was an abrupt and dramatic change in the patient's status. Over a four-hour period she voided more than 2,000 cc. of urine and associated with this there was rapid subsidence of her skin eruption, diarrhea, dyspnea and abdominal pain. The raies in the right lung cleared and she was able to maintain a blood pressure of 110/70 mm. Hg without continuous intravenous vasopressors. She continued to show improvement throughout the next day and was removed from the oxygen tent. For somewhat over a week thereafter her appetite was good; she showed no further rash or respiratory symptoms, and was free of diarrhea and abdominal pain. However, on August 7, there was a recurrence of symptoms with a fall in blood pressure to 78/40 mm. Hg, tachycardia, skin manifestations, vomiting, abdominal pain, diarrhea, excessive lacrimation and dyspnea. Fever was absent. The leukocyte count was found to be 25,500 per cu. mm. with a moderate shift to the left in the differential count. She was again placed in an oxygen tent and given continuous intravenous levarterenol, together with ephedrin orally. On this occasion auscultation of the heart revealed a rough, grade 2 to 3 systolic murmur over the pulmonic area. There was questionable ascites and the neck veins were markedly distended. After four days in the oxygen tent and continuous intravenous levarterenol, the patient gradually became able to maintain her blood pressure above shock levels without vasopressor medication. The attack subsided.

On August 15, pitting bilateral pretibial edema as well as edema of the forearms was noted. The pulse rate at this time was 120 per minute, and regular. The right lung was free of râles. The patient was then given a low salt diet. On August 22, following the intramuscular administration of a mercurial diuretic, there was a large diuresis with a loss of 9 pounds in weight. On August 25, analysis of a twenty-four-hour urine specimen for 5-HIAA yielded a value of 51 mg.\* (normal, 2 to 9 mg. per twenty-four hours).

On August 29, at which time the patient stated that her normal menstrual period was expected, an attack again occurred, and was similar in every respect to

\* The authors are indebted to Drs. Sidney Udenfriend and Albert Sjoerdsma of the National Heart Institute, Bethesda, Md., for this initial determination of the urinary 5-HIAA level, and for their continued interest in this case. the previous episodes. On September 1, she was given 0.25 mg. of ergotamine tartrate twice with an interval of three hours between doses. The second dose was followed by precordial pain; therefore, no further administration of the drug was undertaken. At this time, electrocardiogram showed S-T segment and T wave changes. On the following day the attack abruptly subsided.

On September 6, skin manifestations recurred. At this time 0.25 mg. of ergotamine tartrate was administered intramuscularly. On the following day her rash subsided and no other signs or symptoms typical of her attacks appeared. On September 7, analysis of a twenty-four-hour collection of voided urine for 5-HIAA yielded a value of 147 mg. per twenty-four hours. On September 8, a typical attack occurred; at this time the pulse rate was 110 and a systolic gallop was heard as well as the previously noted systolic murmur over the pulmonic area. A twenty-four-hour urine specimen collected during this day yielded a value for 5-HIAA of 187 mg. per twenty-four hours. Twenty-four hours later moderate improvement in symptoms was noted, and by September 12, she was entirely asymptomatic.

On September 13, because of the suggestion of a temporal relationship between the onset of her attacks and her menses, the patient was given 0.8 cc. of progesterone intramuscularly in an attempt to provoke

an attack. No attack occurred.

On September 15, administration of raudixin® 50 mg. four times a day, was started. On September 19, a palpable systolic thrill was noted over the pulmonic area. There were no signs of congestive failure. The blood pressure was 110/60 mm. Hg, pulse 100. However, by September 21, definite signs of predominantly right-sided congestive failure appeared. On the following day a 7 pound weight loss accompanied a diuresis following intramuscular administration of a mercurial diuretic. A twenty-four-hour urine specimen yielded a value of 5-HIAA of 102 mg. per twentyfour hours; two days later a value of 149 mg. per twenty-four hours was obtained. During the following week the patient showed rather marked improvement. Her appetite was excellent; diarrhea, nausea, vomiting, abdominal pain, skin rash and lacrimation all subsided almost completely and she seemed much stronger. For the first time since her hospitalization she was able to ambulate and on September 30, fifteen days after it had been started, raudixin therapy was stopped. On this day the patient was allowed to leave the hospital for several hours for an auto ride with her husband, and to eat dinner outside of the hospital. On the following day all of the preceding symptoms and signs of a typical attack rather abruptly appeared, in addition to grossly audible wheezing respirations and marked dyspnea. Her pulse rate was regular at 116 per minute and the blood pressure was 90/50 mm. Hg. She was again placed in an oxygen tent and given levarterenol intravenously. In addition, she received

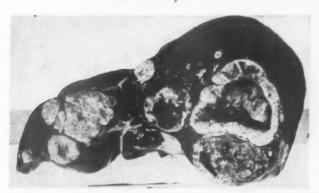
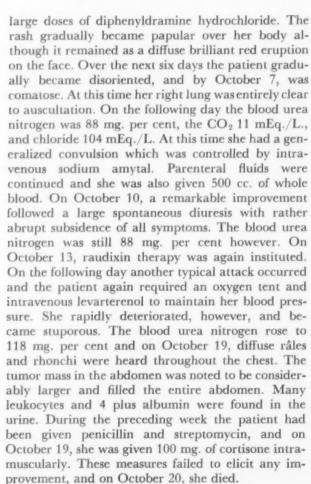


Fig. 3. A section through the enlarged liver, showing numerous metastatic nodules, some with central necrosis and cyst formation.



In addition to the medications already mentioned, and particularly at various times during her attacks, she had also received the following medications without any apparent beneficial effect: paregoric, deodorized tincture of opium, meperidine, prostigmine, aminophylline, ascorbic acid and prolonged large doses of B-complex vitamins.

At autopsy, the left pleural space in the thoracic cavity was obliterated by fibrous adhesions and the left lung was absent. The right pleural space was free

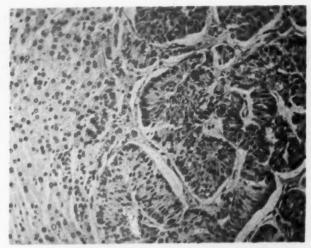


Fig. 4. The border of a nodule of metastatic carcinoid tumor in the liver and adjacent normal hepatic parenchyma. Hematoxylin and eosin stain, original magnification × 260.

of fluid and adhesions. The right lung was well expanded. Marked congestion of the lower lobe was present. Frothy secretions were in the bronchial tree. In the lower lobe, and to a lesser degree in the middle lobe, numerous areas of bronchopneumonia were present. The mediastinal lymph nodes appeared normal.

In the abdominal cavity, the peritoneal surface appeared unremarkable. The liver extended 8 cm. below the right costal margin and weighed 2,650 gm. Its surface was nodular. On cut section, numerous tan-white tumor masses were scattered throughout the parenchyma. The largest of these nodules measured 8 cm. in diameter. Many of the nodules showed central necrosis with cyst formation. (Fig. 3.) The spleen weighed 95 gm. and on cut section was seen to contain numerous small yellow-tan nodules scattered throughout. The largest measured 0.5 cm. in diameter. The right kidney weighed 170 gm. and the left kidney weighed 250 gm. On the left, the capsule stripped off with ease to reveal a pale smooth surface. Cut section of the left kidney showed a thick pale cortex with prominent cortical-medullary demarcation. The medullary pyramids appeared dark reddish purple and contrasted markedly with the pale cortex. The capsule of the right kidney was moderately adherent and numerous coarse scars were present over the surface of the kidney. These scars involved the entire cortex and medulla and distorted the pelvis. A small cyst was present at the upper pole of the right kidney.

Careful scrutiny of the esophagus, stomach, small intestine, colon, appendix and rectum failed to reveal any intrinsic lesions. Small carcinoid tumors, in particular, were sought and none were found. The pelvic organs were grossly normal. Enlarged periaortic lymph nodes were noted and on cut section appeared to contain tumor. A single peripancreatic

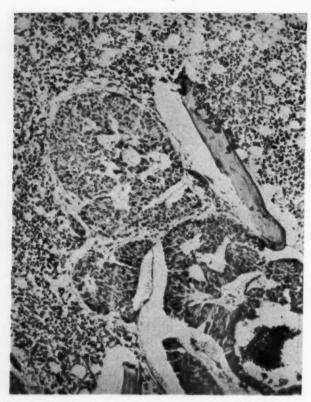


Fig. 5. Vertebral bone marrow containing nodules of metastatic carcinoid. Hematoxylin and eosin stain, original magnification × 100.

lymph node measuring 2 cm. in diameter also appeared to contain tumor with necrosis in its center. The pancreas, adrenal glands, bones and joints, soft tissues, central nervous system and heart all appeared grossly normal.

On microscopic examination, severe bronchopneumonia with microabscess formation was noted in the right lung. In the liver, numerous nodules of metastatic tumor with the histological characteristics of carcinoid were noted. (Fig. 4.) Argentaffine granules could not be demonstrated by the appropriate staining technic. Nodules of metastatic tumor were present in the spleen. In the kidneys, severe degeneration of the epithelium of the proximal convoluted tubules was present and the epithelial cells contained huge vacuoles. The nuclei were absent from many cells. The lymph nodes examined contained metastatic tumor with areas of necrosis. Vertebral bone marrow contained numerous nodules of metastatic tumor. (Fig. 5.) The remaining organs examined including the heart appeared histologically normal.

The tumor was observed to be composed of cords of ribbon-like cells, columnar in appearance and having regular nuclei of a somewhat fusiform shape surrounded by abundant eosinophilic cytoplasm. The cells tended to line up in palisade formation. Numerous cystic spaces were present in the tumor and were filled with a mucoid material; however, no true glandular spaces were formed. While this tumor bore

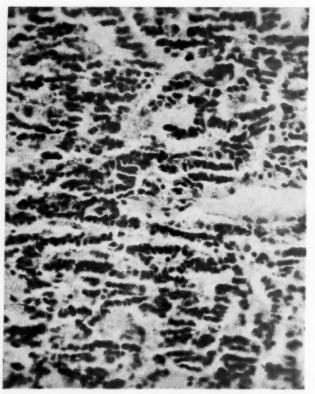


Fig. 6. Section of the original lung tumor. Although the section is thick and staining technic is different, the histologic pattern of this tumor appears strikingly similar to that of the metastatic carcinoid involving the liver, spleen, lymph nodes and bone marrow. Hematoxylin and eosin stain, original magnification × 300.

some resemblance to adenocarcinoma, it appeared more similar to carcinoid. Only one section from the previously resected lung tumor was available, but certainly showed sufficient similarity to the metastatic tumor involving the liver, spleen, abdominal lymph nodes and bone marrow to be considered the same neoplasm. (Fig. 6.) Although the pattern of the tumor was not entirely typical of bronchial adenoma of the carcinoid type, it was similar enough to come within the range of morphology of malignant bronchial adenoma.

Case II. S. P., a fifty-five year old white woman, was admitted to The Mount Sinai Hospital, New York City, on December 2, 1957, complaining of episodic flushes of the face, neck and upper thorax during the preceding eight months. Nausea, anorexia and a weight loss of 20 pounds, accompanied these cutaneous manifestations. The exanthem recurred intermittently, usually two or three times a week, lasting from one hour to thirty-six hours. These paroxysms were most frequently precipitated by emotional stress or eating. During the flush, the skin of the face and neck appeared deep red with patches of red discoloration about the upper thorax. In these areas there was a sensation of local heat and tightness accompanied by

periorbital and facial edema, excessive lacrimation and "burning of the eyes," palpitations, and slight dizziness on standing. On these occasions, she was found to have a normal blood pressure.

One month prior to admission, during a rather prolonged episode of flushing, she experienced the onset of severe explosive diarrhea consisting of six to eight watery stools per day. This was accompanied by mild abdominal cramps without fever or melena. The diarrhea persisted for about one week and did not

subsequently recur.

The patient had previously been admitted to The Mount Sinai Hospital, on February 7, 1949, for removal of a nodule in the left breast. It was then also intended to evaluate an asymptomatic lung shadow originally detected by a routine survey photofluorogram. At that time (1949) she related that she had suffered from periodic flushes, sweats and flashes of heat for several years, accompanied by severe "melancholia": the latter was most pronounced about the time of her menstrual periods. These symptoms were attributed by her physician to the onset of her menopause although she was menstruating regularly at that time. Some relief of these symptoms was obtained by the use of estrogen therapy. Physical examination was within normal limits except for a 2 by 2 cm. freely moveable nodule in the lower outer quadrant of the left breast and a saddle nose deformity secondary to previous nasal surgery for chronic sinusitis. There was no hypertension, cardiomegaly, murmurs, abnormal heart or pulmonary sounds, or hepatomegaly. Upon resection, the breast nodule was found to be a fibroadenoma.

Roentgenograms of the chest and sectional radiographic studies showed the lesion previously noted, in the left lower lobe. The findings on bronchoscopy were within normal limits. No tumor cells were seen in the bronchial washings nor were tubercle bacilli found on smear or culture. Neoplasm of the lung was suspected and an exploratory thoracotomy was performed. In the apical segment of the left lower lobe an indurated area, approximately 6 by 4 cm., was found surrounding a cavitary lesion filled with thick purulent material. A segmental resection was performed, with removal of about one-third of the involved lobe. Microscopic section revealed a suppurative bronchopneumonia, bronchiectasis and a chronic lung abscess surrounded by multiple small abscesses. The patient's postoperative course was uncomplicated and she was discharged on March 3, 1949.

Subsequently the patient had few pulmonary complaints except for occasional cough productive of small amounts of whitish mucoid sputum and mild dyspnea on exertion. Although she was not conscious of any adventitious sounds, examination of the chest on several occasions revealed bilateral high pitched musical wheezes which increased on forced respiration. She was given bronchodilator therapy without alteration in symptoms. In addition her menstrual periods,

which had previously been regular, became irregular in 1951 and stopped entirely in the latter part of that year. However, she continued to experience periodic flushes and sweats, despite continued estrogen therapy, until 1953 when the symptoms gradually ceased. The severe melancholia previously noted persisted although it became less marked after 1953.

In June 1952, an acute coryza developed associated with severe cough productive of purulent sputum. Roentgenogram of the chest revealed a shadow in the anterior part of the left upper lobe and she was advised to return for follow-up studies. She neglected to do this until September 1952 when roentgenograms demonstrated atelectasis of the left upper lobe. Bronchoscopy revealed "a granular friable mass" obstructing the left upper lobe bronchus. Microscopic diagnosis of the biopsy obtained from the mass was reported as "adenocarcinoma." The patient was again admitted to The Mount Sinai Hospital on September 22, 1952 for definitive surgery. Physical examination disclosed dullness to percussion and bronchial breath sounds over the left upper lung field anteriorly and posteriorly. A grade 2 to 3 harsh systolic murmur was heard, loudest at the second intercostal space to the left of the sternum, without an associated thrill. There was no cardiomegaly, evidence of congestive heart failure or hepatomegaly. On October 1, 1952, left pneumonectomy was performed. Examination of the resected specimen disclosed a polypoid mass of tumor tissue arising from the left upper lobe bronchus and involving the adjacent lymph nodes. (Figs. 7, 8 and 9.) Microscopic examination appeared to confirm the biopsy findings of adenocarcinoma. The adjacent lymph nodes were infiltrated by "malignant cells" and the surrounding lung tissue showed bronchiectasis, fibrosis, and acute and chronic inflammation. The patient's postoperative course was complicated by transient auricular fibrillation successfully converted to regular sinus rhythm by quinidine. She was discharged from the hospital on October 16, 1952.

In September 1953, during a follow-up clinic visit, the patient's liver was found to be enlarged to 3 finger-breadths below the right costal margin. The physical examination was otherwise unchanged.

In respect to family history, it may be pertinent that the patient's son had been institutionalized at fourteen years of age for dementia praecox and remained in an institution until his death at twenty-nine years of age. The cause of death was listed as "bowel obstruction." Postmortem examination revealed "congenital megacolon."

Examination upon admission to The Mount Sinai Hospital in December, 1957 showed the patient to be a well developed, well nourished white woman in mild respiratory distress. She exhibited moderate emotional lability but was oriented and cooperative. Her weight was 155 pounds, the oral temperature was 99.6°F., the radial pulse was regular at 110/minute, and the blood

pressure was 100/70 mm. Hg. The patient's face and neck were swollen and appeared fiery brick red. The skin over the thorax displayed a mottled red discoloration. Occasional telangiectasia were noted about the face. The areas of discoloration were hot to the touch and slightly tender. She had marked conjunctival injection with increased lacrimation. The visible mucous membranes of the nose and mouth also were bright red. The neck veins showed no filling at a body position of 45 degrees. No significant adenopathy was present. The skin of the extremities was moderately dry but not pigmented. She had no glossitis or cheilosis. A well healed thoracotomy scar was present; a portion of the fourth rib on the left had been removed. Breath sounds were absent and the percussion note dull over the left hemithorax. Over the right hemithorax a hyperresonant percussion note was elicited and breath sounds were normal. The heart was not enlarged. A forceful apex beat was felt in the fourth intercostal space at the mid-clavicular line. A grade 3 holosystolic harsh murmur was heard in the third intercostal space just to the left of the sternum and was transmitted upwards and throughout the entire precordium. There was an associated thrill in the same area. P2 was slightly decreased in intensity. The liver was palpable 5 fingerbreadths below the right costal margin. It was non-tender with a somewhat nodular surface. The bowel sounds were normal.

Laboratory studies disclosed normal values for hemoglobin, white cell count and differential, blood serologic tests, urinalysis, blood urea nitrogen, fasting blood sugar, uric acid, total serum cholesterol, platelet counts, prothrombin time, bleeding and coagulation time, serum electrolytes, blood 17-OH corticoids and twenty-four-hour urinary excretion of 17-ketosteroids. No occult blood was found in the feces. A sulfobromophthalein test and other tests of liver function also gave normal results, as did measurements of the venous pressure and circulation time.

As a rapid test for identification of large amounts of 5-hydroxyindole acetic acid (5-HIAA) a sample of urine was mixed with equal amounts of Ehrlich's reagent [37]. A positive reaction was obtained, a dark blue color appearing in four hours. Strongly positive tests for 5-HIAA were also obtained on four occasions by the direct color reaction with 1-nitroso-2-naphthol as reagent [15]. The blood serum serotonin level determination was 1.5  $\mu$ g./ml. (normal: 0.03 to 0.20  $\mu$ g./ml.).\*

Roentgenogram of the chest showed postpneumonectomy changes including moderate displacement of the heart to the left in clockwise rotation. Other than mild compensatory emphysema, the right lung appeared to be normal. Serial electrocardiograms were compared: the tracing of September 27,

\*The blood serotonin level was determined in the laboratory of D. W. Woolley, Rockefeller Institute for Medical Research, to whom we are greatly indebted.

1952, shortly following the left pneumonectomy was normal. The electrocardiograms of September 28. 1956 showed increased R wave amplitude in V2 and V<sub>3</sub>, with a further increase in the tracing of December 9, 1957. The latter also showed low T waves in V4 to V<sub>6</sub>. A vectorcardiogram was oriented inferiorly and somewhat anteriorly. Its rotation in the horizontal plane was counterclockwise. The electrocardiographic and vectorcardiographic changes were interpreted as representing either the effect of rotation or of right ventricular hypertrophy, or both. A phonocardiogram recorded over the pulmonic area and to the left of it registered a diamond-shaped holosystolic murmur of moderately high amplitude, as seen in valvular stenosis of either the aortic or pulmonic orifice. The second pulmonic sound was reduplicated.

Sigmoidoscopy demonstrated normal appearing mucosa in the rectum and lower sigmoid. Roentgen studies of the gastrointestinal tract from the esophagus to the rectum, including fortuitous visualization of the appendix, disclosed no intrinsic or extrinsic abnormalities.

During the patient's three week hospitalization she manifested four major and three minor flushing episodes varying in duration from thirty-six hours to one hour. These were effectively ameliorated by oral administration of promazine. No diarrhea or asthmatic episodes occurred. Needle biopsy of the liver was performed and carcinoid tissue similar to that in the lung was found.

The history of paroxysmal flushing, diarrhea and weight loss, and the findings of hepatomegaly and acquired right-sided heart disease indicated the diagnosis of functioning carcinoid syndrome. The demonstration of markedly increased urinary excretion of 5-HIAA and an increased serum level of serotonin confirmed the clinical impression. In view of the diagnosis five years previously of bronchial carcinoma with regional lymph node involvement, the long survival of the patient without deterioration (other than what could be attributed to the functioning carcinoid syndrome) seemed most atypical. In addition, the failure to demonstrate a tumor in the gastrointestinal tract, and the experience with the first case, led to re-evaluation of the histologic diagnosis of the previously resected lung tumor. Re-examination proved the tumor to be a bronchial adenoma of the carcinoid type with regional lymph node involvement. (Figs. 7, 8 and 9.) Unfortunately it was not technically feasible to apply silver stains to the material reviewed.

## COMMENTS

Of the various manifestations of the functioning carcinoid syndrome, the most frequently occurring are: cyanotic flushes with hypotension, diarrhea, respiratory distress, enlarged liver, and increased urinary 5-HIAA. The cardiac changes usually occur late in the clinical course

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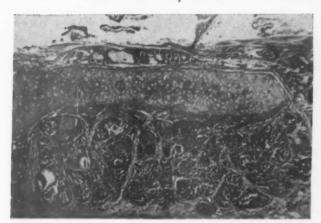
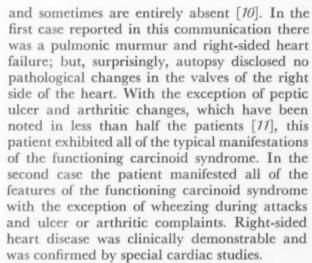


Fig. 7. Tumor tissue in the wall of the bronchus with infiltration around and beneath the bronchial cartilage. Hematoxylin and eosin stain, original magnification × 25.



Many of the manifestations occurring in this syndrome are the direct result of the excessive serotonin produced by these tumors [12]. No condition other than malignant carcinoid has been found to cause excessive urinary excretion of 5-HIAA [13,14]. Hence the relatively simple qualitative test for urinary 5-HIAA [15] is highly specific for metastatic carcinoid and when positive may be considered pathognomonic.

Attempts were made to control or abort the first patient's paroxysmal attacks with various substances (ergot derivatives, diphenyldramine hydrochloride, chlorpromazine, atropine and a rauwolfia preparation) which pharmacological studies have suggested as acting antagonistically, blocking or being antimetabolic to serotonin [7,16–19]. Diphenyldramine hydrochloride, chlorpromazine and atropine produced no apparent beneficial effect. On two occasions during the first day of typical attacks relatively small doses

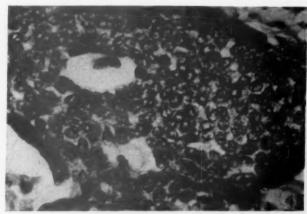


Fig. 8. A section demonstrating the cellular characteristics of the tumor. Interlacing sheets and cords of uniform cells are seen with round vesicular nuclei showing little hyperchromatism and atypism and rare mitotic figures. In some areas a reticular pattern typical of the carcinoid form of bronchial adenoma is displayed. Hematoxylin and eosin stain, original magnification × 400.

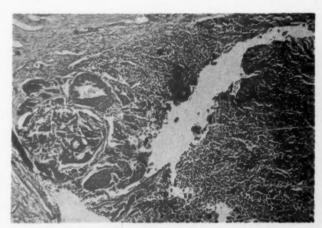


Fig. 9. A section showing invasion of an hilar lymph node by the tumor. Hematoxylin and eosin stain, original magnification  $\times$  60.

of ergotamine tartrate were given. One attack terminated prematurely and the other improved within twenty-four hours. Nevertheless, the authors are inclined to view this as coincidental and spontaneous rather than the result of such relatively small dosage. Rauwolfia when given to experimental animals has been found to mobilize serotonin from the intestine and to increase its excretion in the urine as 5-HIAA [20]. Hence, a course of raudixin was given for more than two weeks. During this time, although there was no significant alteration in the urinary excretion of 5-HIAA, marked symptomatic improvement was apparent. During this fifteenday period the patient was free of even mild cutaneous, respiratory and gastrointestinal symptoms whereas during the preceding several months she had not been free of symptoms for any period longer than five to eight days. Moreover, a typical attack occurred soon after withdrawal of raudixin, so this drug may have produced some degree of beneficial response. In the second case the severity and frequency of the patient's paroxysmal episodes were di-

minished by promazine.

Bronchial adenoma, although infrequently encountered, should not be categorized as rare. It comprises approximately 5 per cent of all bronchial neoplasms detected by bronchoscopy [21]. Classification of the several types of bronchial adenomas has been somewhat confusing because of the use of different terminology by various authors; the simplest and perhaps most widely accepted classification is that of Hamperl [22]. Based on the histological appearance of these tumors he divided bronchial adenomas into two major types, cylindromas and bronchial carcinoids. Liebow states that approximately 15 per cent of bronchial adenomas are of the cylindroma type, and approximately 85 per cent are of the carcinoid type [23]. For many years these tumors were not considered to have malignant potential, and as recently as 1941 Foster-Carter in a review of bronchial adenoma stated that these tumors were entirely benign [21]. Since that time, however, there have been many reports of bronchial adenoma metastasizing to regional lymph nodes, liver, bone marrow and other organs [24-32]; nevertheless, the occurrence of distant metastasis from a bronchial adenoma remains an infrequent finding.

The cellular genesis of bronchial adenoma is not known with certainty but the most prevalent hypothesis is that these tumors arise from the bronchial glands. Foster-Carter suggested that these tumors are identical in nature with salivary gland tumors arising from the bronchial glands [27]. Stout considered the possibility of bronchial adenoma arising from the oncocyte [33], a peculiar cell found in the glands and glandular ducts of adult human bronchi. Womack and Graham, however, suggested that bronchial adenomas result from embryonic bronchial buds which have failed to develop normally [34]. Another hypothesis proposed by Jackson and Konzelmann [35] has been given little consideration in recent years but now seems particularly intriguing. They considered the possibility that these tumors might be related to the true carcinoid (argentaffinoma) of the gastrointestinal tract and derive from neural elements in the bronchi.

Hamperl applied the term bronchial carcinoid to one of the two major types of bronchial adenoma because of the histologic similarity between this tumor and the intestinal carcinoid. However, differences were also seen, the main one being the inability to demonstrate, in bronchial carcinoids, the presence of the silverstaining granules [22] characteristically found in gastrointestinal tract carcinoids. Jackson and Konzelmann could not demonstrate argentophile staining characteristics in the cases of bronchial adenoma they studied [35], nor could Anderson in his case [28]. A group of bronchial adenomas studied by Stout also failed to exhibit silver-staining granules [33], as did a number of these tumors studied by Rabin [35]. Of thirty-four bronchial adenomas in which the stain was attempted, Holley demonstrated argentaffin granules in one [30]. A review of the literature indicates this to be the only reported instance in which argentaffin granules have been demonstrated in bronchial carcinoid. The failure of this tumor to exhibit argentophile characteristics has been the main reason for lack of credence in the existence of a relationship. other than a coincidental histological similarity, between it and the true carcinoid.

In the first case reported in this communication the carcinoid syndrome appeared to result from metastatic, carcinoid type, bronchial adenoma. In the second case the functioning carcinoid syndrome also appeared to result from a bronchial adenoma, carcinoid type, with hepatic metastases; the presence of the hepatic metastases has been histologically proved. One wonders if the functioning carcinoid syndrome has occurred unrecognized in previously reported cases of metastatic bronchial adenoma. In 1956 Kincaid-Smith and Brossy [32] reported a case in which, six years after lobectomy for bronchial adenoma, a liver metastasis was found, and at that time the patient complained of severe intermittent watery diarrhea and borborygmi of ten weeks' duration. Unfortunately, urinary studies for 5-HIAA were not performed.

In view of the two cases herein reported it appears probable that the relationship between primary bronchial carcinoid and gastrointestinal tract carcinoid is more than coincidental and that the association between bronchial adenoma and the functioning carcinoid syndrome represents a distinct clinical entity.

#### SUMMARY

1. The clinical and laboratory findings in two cases of the functioning carcinoid syndrome associated with bronchial adenoma are presented. In the first case autopsy findings are included and metastatic involvement of the liver was demonstrated.

2. Rauwolfia therapy appeared to produce some degree of improvement in the manifestations of the functioning carcinoid syndrome in the first case reported. Therapeutic attempts with various other substances produced no significant clinical improvement. In the second case improvement resulted from promazine therapy.

3. A brief discussion of various aspects of bronchial adenomas, including a number of hypotheses on the origin of these tumors, is presented.

4. It is proposed that cases of metastatic bronchial adenoma be scrutinized for the carcinoid syndrome because of the apparent ability of metastatic bronchial adenoma to produce this syndrome.

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# New Concepts in the Evaluation of Intersex and Infertility\*

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It is now accepted that the sex of an individual is recognizable from the morphological characteristics of the somatic cells, so that by examining a small specimen of almost any tissue it is possible to say whether the patient is male or female. This is called the "chromatin sex." This noteworthy discovery, made by Barr and his group [1,2], has yielded information which prompts re-appraisal of many embryological concepts and a more modern interpretation of the different endocrinopathies. Our own experience in the endocrine clinic and the large number of articles currently appearing in the medical literature indicates that problems of unknown sex are very much more common than is generally realized.

With the development of newer technics in medicine, it often appears that certain problems of diagnosis, treatment and prognosis are about to be made infinitely easier. Many times, however, this expectation is not fulfilled, for the newer diagnostic methods create more profound problems and make the treatment and management of the relevant abnormalities even more difficult and perplexing. This is perhaps particularly true of the recently developed chromatin sex test, which is dependent either upon condensation of nuclear material at the peripheral border of the nucleus of tissue cells taken by biopsy or by scrapings from the mucosal surfaces of the body or upon condensation of nuclear chromatin in the form of a "drumstick" in the polymorphonuclear neutrophil. Results derived by these technics have raised questions regarding the etiology of certain syndromes, and while on the surface they have appeared to explain some known inconsistencies, they have

also led to uncertainty in the management of patients whose sex chromatin pattern seemed to contradict the clinical and apparent physical sex of the individual. The atmosphere of bewilderment is gradually clearing, however, and much useful information has been accumulated.

Our own studies have consisted principally of observations on the nuclei of polymorphonuclear neutrophil leukocytes, enlarging upon the original findings by Davidson and Smith [3] with respect to normal persons. We are confident of the reliability of the blood smear in this type of investigation and have developed and described refinements of its interpretation in a study of normal and abnormal subjects [4,5]. Although certain difficulties with the method have been described, there is nevertheless a growing body of literature on the subject, all of which is confirmatory of the leukocyte's general dimorphism [6-9]. Chromatin studies divide subjects into two groups whose tissues are, according to Barr's terminology: "chromatin positive" i.e., presence of the particular chromatin condensation (as in normal females) and "chromatin negative" where no such structure is observed (as in normal males). In addition, the information derived from the blood smear also possesses quantitative aspects that may have some important clinical diagnostic value which is unobtainable from examination of the cells of other tissues [10]. The leukocyte is a convenient cell to examine and the blood smear may also furnish other information of endocrinological interest which we are now exploring.

Whenever we have studied various tissues from the same patient, the same sex pattern in the cells of all the tissues studied (blood, skin, oral

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TABLE I SUMMARY OF THE FINDINGS IN THE ELEVEN PATIENTS DISCUSSED IN THE TEXT

Case	Diagnosis	Clinical Sex	Chromatin Sex	Value of Chromatin Sex
I	Gonadal aplasia in a male	Male	Female (positive)	Indicates infertility
11	Gonadal dysgenesis	Female	Male (negative)	Makes diagnosis; indicates infertil
III	Gonadal dysgenesis	Female	Female (positive)	None
IV	Congenital adrenogenital syndrome	Male	Female (positive)	Aids diagnosis; important in reas- signing sex; suggests fertility
v	Juvenile Klinefelter's syndrome	Male	Female (positive)	Makes diagnosis; indicates infertil- ity
VI	Indeterminate sex	Female (chosen)	Male (negative)	Indicates infertility as a female
VII	Indeterminate sex	Female (chosen)	Female (positive)	Endorses choice of sex
VIII	Adrenogenital syndrome	Female	Female (positive)	Indicates fertility; aids diagnosis
IX	Klinefelter's syndrome	Male	Male (negative)	None, although of great interest
x	Indeterminate sex	Female (chosen)	Female (positive)	Endorses choice of sex; avoids laparotomy
XI	Klinefelter's syndrome	Male	Female (positive)	Makes diagnosis; indicates infertil- ity

mucosa, biopsied organs) has always been found and we know of no instance in the literature in which the chromatin sex was at variance in the different tissues of the same subject. Wiedmann et al. [9] found difficulties in this respect but they were able to resolve them in all cases. Furthermore, it should be emphasized that there is no report of any functioning testis in a chromatin-positive subject or of a functioning ovary in a chromatin-negative subject.

The value of chromatin sex determination is greatest in patients with infertility or with failure of development of the secondary sex characteristics. For instance, it has been reported from various centers [11,12] that a proportion of patients, formerly classified as having Turner's syndrome or ovarian agenesis and now perhaps correctly labeled gonadal dysgenesis, show the male sex chromatin pattern. This is of more than academic interest. We now have strong grounds for supposing that a patient with primary amenorrhea who shows this pattern must be considered infertile and in need of replacement therapy with any of the many appropriate steroid hormone preparations now available. Without complex chemical studies or laparotomy, one can now assume that if an overt female shows the male chromatin sex pattern there is an absence of gonadal tissue or at least, if gonadal tissue is present, it is incapable of producing a gamete. Consequently, the patient must be considered to be irreparably infertile. Here then is a test of fertility of utmost importance and of high accuracy which involves no more elaborate technic than a good differential white cell count. Once the diagnosis is established, prompt institution of replacement therapy with the required sex steroid would prepare the patient for all aspects of her feminine role except that she would never bear children.

This new dimension in the appraisal of a patient's sex is also useful in the study of intersex. In selected cases the chromatin pattern has been of definite help in planning the course to be taken in the upbringing of children of indeterminate sex. So far, however, application of the knowledge of the chromatin sex to a given clinical problem is difficult and inadequately understood. It must be emphasized, however, that the chromatin sex is merely one piece of evidence which should never be accorded overriding pre-eminence over clinical judgment and experience in the management of any intersex patient. The purpose of this paper is to discuss some of the lessons that have been learned from cases of apparent intersex in which knowledge of the chromatin sex has been available. Eleven cases have been chosen as illustrative examples of some of the principles which have been formulated. (Table 1.)

# TECHNIC

The method which we have employed depends on the findings of Davidson and Smith [3] and employs criteria which we have attempted to derive from studies based on their information [4]. An ordinary

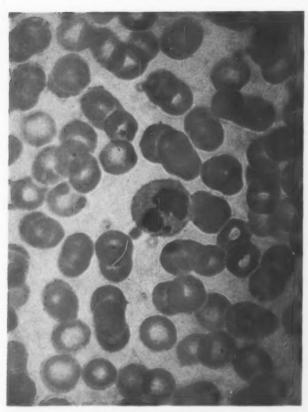


Fig. 1. Neutrophil leukocyte with "drumstick" attached to one of its lobes. Chromatin sex female.

blood smear is prepared, as in making a differential white count. Slides have been used in preference to cover slips. The smear is stained, using tetrachrome or Wright's stain, and is given an arbitrary serial number so that the condition of the examination is entirely objective. The "drumstick" (Fig. 1), a projection of nuclear chromatin which characterizes the female, is rounded, hyperchromatic in appearance, 1.5 microns in diameter and borne on a narrow stem. It is never multiple. It is to be distinguished from smaller projections ("small clubs") (Fig. 2) and from minor lobes of the nucleus (Fig. 3) which are found in both sexes. Sometimes a concentration of chromatin is seen which, although not borne on a stem, has all the other characteristic features of the drumstick; this structure, the "sessile nodule" (Fig. 4), also characterizes the female. Although it may be argued that the finding of one drumstick is enough to make a diagnosis of female sex (chromatin-positive) it has been our practice to continue the examination until six drumsticks have been found. No blood smear is declared to be definitive of the male sex until the examination has proceeded to at least 500 mature neutrophils. When the examination of 500 neutrophils has left any doubt in the observer's mind or when sessile nodules have been seen, it is wise to continue the examination to include at least an additional 500 cells. It is emphasized that although the appearances just described are quite simple to see, interpretation of the smears should

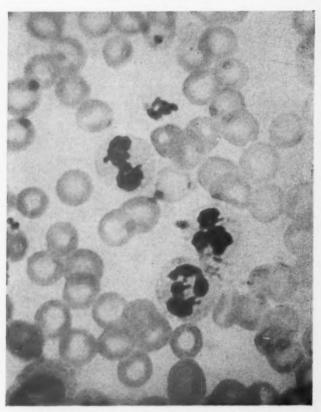


Fig. 2. The "small clubs" which are seen on the leukocytes of both sexes are not to be confused with drumsticks.

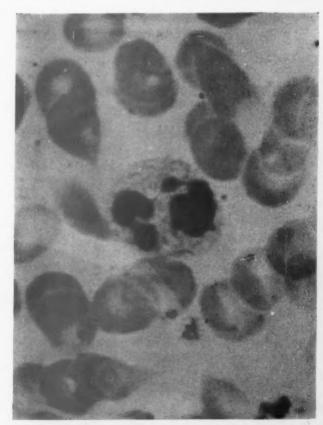


Fig. 3. This leukocyte has a small minor lobe. Either sex.



Fig. 4. One nuclear lobe of this neutrophil shows a "sessile nodule." This probably occurs only in females.

be left to those with considerable experience with the method, especially when the results of the test will lead to the important decisions of the type described in this paper. In all our studies the investigator examining the slide has always been in ignorance of the source of the blood smear. Whenever an important decision has been influenced by the result of the blood smear, a further report has been requested from objective examination of slides subsequently obtained. We believe that, properly performed, this test does not give false results but that taken out of context the results may very easily lead to false conclusions.

CASE 1. Gonadal aplasia in a male (Fig. 5): B. S., a forty-eight year old man was investigated endocrinologically because of eunuchoidal characteristics. He was married but had been unable to sire any children. He had never been seriously ill in his life except for an ever present thrombophlebitis which was the cause of his entrance into the hospital. This peripheral vascular abnormality had been under treatment with anticoagulants. Examination revealed a male with poor secondary sex hair development who shaved infrequently. His beard was minimal, the distributon of hair on the body was rather feminine in character and a female escutcheon prevailed. The voice was high pitched and the pelvis broad. There was no gynecomastia. The skin tended to be somewhat smooth and feminine in character. The heart, lungs and abdomen were within normal limits. Muscular development was adequate. The genitalia consisted of a penis of normal size with a redundant, fairly well developed scrotum containing two small testis-like structures which were firm, hard and nontender and about the size of peas. The extremities were normal except for the peripheral vascular disease already mentioned. Hormone assays revealed the following: Urinary gonadotropic hormone excretion (FSH), greater than 105 mouse units per twenty-four hours; 17-ketosteroids, 15.3 mg. per twenty-four hours; protein-bound iodine, 5.1 gamma per cent; glucose tolerance test, essentially normal. A testicular

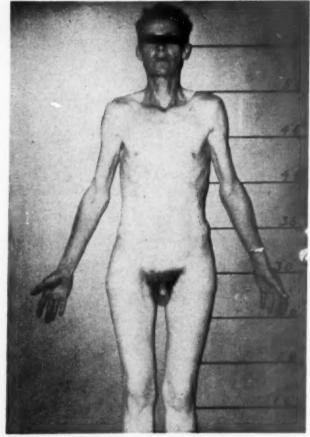


Fig. 5. Case I. Gonadal aplasia in a male. Chromatin sex positive (female).

biopsy specimen revealed nondescript tissue the identity of which could not be established and certainly could not be classified as either ovarian or testoid in character. The patient responded adequately to steroid hormone therapy by increase in weight, development of muscular size and strength and accentuation of sex drive. The blood showed the chromatin-positive (female) pattern. It is clear that at this age and in these circumstances there is no place whatever for any attempt to induce a profound change in the endocrine system. Early demonstration of the clinical picture, however, might have resulted in institution of androgenic therapy and would have reversed the obvious feminine qualities which the patient now presents-his high-pitched voice, feminine habitus, smooth skin, etc.

CASE II. Gonadal dysgenesis (Fig. 6): B. W. was a twenty-six year old woman who underwent a full investigation for primary amenorrhea. Her psychological orientation was entirely feminine. Physically she was female although the secondary sexual characteristics were somewhat underdeveloped. The external genitalia were normal except for some enlargement of the clitoris. A markedly hypoplastic uterus was found on rectal palpation. The vaginal

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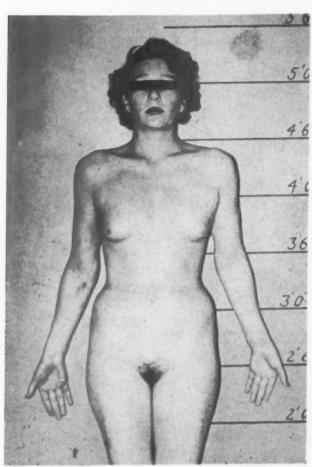


Fig. 6. Case II. Gonadal dysgenesis. Chromatin sex negative (male).

smear was of the castrate type. The urinary gonadotrophic hormone excretion was greater than 105 mg. per twenty-four hours. The protein-bound iodine was 5.9 gamma per 100 ml. These data were considered to be overwhelming evidence of the absence of ovaries. Her secondary sexual characteristics, which were undoubtedly more developed than is usual in this syndrome, had responded somewhat to prior endocrine therapy with sex steroid because of amenorrhea. The diagnosis was confirmed by the experience that the patient showed no response to gonadotrophic hormone therapy. Menstruation was subsequently induced by the therapeutic use of estrogen and progesterone but not by progesterone alone. The blood smear showed an entire absence of "drumsticks" on the nuclei of the neutrophils and was therefore indistinguishable from that of the normal male.

CASE III. Gonadal dysgenesis (Fig. 7): E. M. C. was first seen at the age of nineteen years when she was admitted to Bellevue Hospital with rheumatoid arthritis primarily affecting her hands. She was referred to the endocrine clinic because of primary amenorrhea and failure of development of secondary sex characteristics. Physical examination at that



Fig. 7. Case III. Gonadal dysgenesis. Chromatin sex positive (female).

time revealed a young female with a child-like face, lack of axillary and pubic hair, no significant breast development and immature external genitalia. She also had cubitus valgus. Rectal examination revealed a small hypoplastic fundus. The state of the adnexa could not be established. Laboratory evaluation revealed the following: Urinary gonadotropic excretion (FSH), greater than 105.6 mouse units per twenty-four hours; 17-ketosteroid, 10 mg. per twentyfour hours; basal metabolic rate, normal; carbohydrate tolerance test, normal; x-ray, except for the arthritic changes, not significant. She showed no significant response to administration of pregnant mares' serum, consisting of 500 I.U. three times a week for three weeks, and failed to menstruate following administration of progesterone either alone or after priming with pregnant mares' serum. However, she did have a very adequate menstrual period following cyclic therapy with estrogen and progesterone. Culdoscopic examination revealed no detectable ovarian tissue. The blood smear showed the chromatin sex of the female with numerous "drumsticks" on the neutrophils. The significance of this large number of drumsticks will be discussed.

CASE IV. Congenital adrenogenital syndrome (Fig. 8): J. S., a fourteen day old infant who was considered by the parents to be a boy, was studied because of the presence of a large phallus, failure to gain weight and some evidence of dehydration. In the family history it was noted that one sibling, born some four years before, had been diagnosed as a pseudohermaphrodite and had died in infancy. There was a normal two year old sibling with no apparent endocrine dyscrasia. Examination of the patient revealed a mildly de-



Fig. 8. Case iv. Congenital adrenogenital syndrome. Chromatin sex positive (female).

hydrated infant with some increase of pigmentation in the area of the scrotum and a large phallus with a urinary meatus opening into its inferoanterior portion. Clinically the patient showed evidence of infantile hypoadrenocorticoidism. The scrotum was well developed and redundant but no scrotal content could be identified. The 17-ketosteroid excretion was found to be 6.8 mg. in twenty-four hours. After treatment with 10 mg. of cortisone per day for one week this decreased to 2.2 mg. per twenty-four hours. The chromatin sex pattern of this child was that of a female. As a result of our studies we advised the parents that the child should be raised as a girl rather than as a boy. The findings of the blood smear were invaluable in this case both with regard to diagnosis and as evidence favoring the patient's future fertility as a female. Subsequently autopsy demonstrated the accuracy of this diagnosis by revealing the presence of a normal female generative tract.

Case v. Juvenile Klinefelter's syndrome (Fig. 9): G. K., fourteen years old, was admitted to the endocrine clinic during an investigation of mental retardation. Physical examination revealed a tall, well developed lad with normal measurements and proportions. There was minimal false gynecomastia. The penis was well developed but both testes were small, firm, hard and high up in the scrotum. Pubic

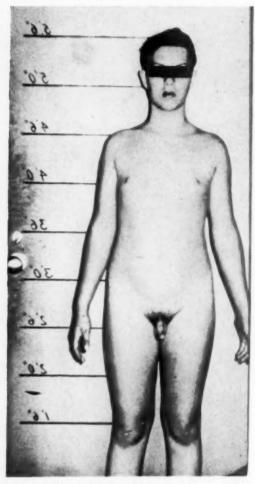


Fig. 9. Case v. Juvenile Klinefelter's syndrome. Chromatin sex positive (female).

hair was present but axillary hair was absent. Because of these clinical findings the patient was evaluated for the possibility of early Klinefelter's syndrome. Laboratory findings included urinary gonadotrophin excretion, between 26 and 52 mouse units per twenty-four hours; 17-ketosteroid excretion, 7.0 mg. per twenty-four hours; protein-bound iodine; 3.3 gamma per 100 ml.; glucose tolerance test, normal. A testicular biopsy specimen (Fig. 10) revealed hyalinization of the basement membrane of the tubules with no evidence of spermatogonia or secondary or primary spermatocytes. The smear of the polymorphnuclear leukocytes showed the female chromatin pattern.

We consider that the blood smear examination in this instance permitted a diagnosis which would not otherwise have been made until some later time in the patient's life. While infertility in this mentally retarded lad would cause little or no problem, in a normal child it would definitely be of importance, for at some later age it would be necessary for him to be acquainted with his defects and to provide accordingly. In addition, this early diagnosis in a young patient not endowed with a normal penis would



Fig. 10. Case v. Testicular biopsy specimen. Hyalinization of basement membrane. No spermatogonia or secondary or primary spermatocytes.

demand the early administration of androgenic substances. While such patients cannot reproduce, due to their endogenous defect, judicious exogenous application of steroid hormone would enable them to assume their proper social and sexual status as normally developed males.

CASE VI. Indeterminate sex (Fig. 11): M. C. was a six month old infant who was being raised as a girl. She was brought to the clinic by the parents because of enlargement of the clitoris. The vulval folds were small and there was a minute vaginal orifice. The excretion of 17-ketosteroids was normal (less than 1 mg. per twenty-four hours). Examination of the blood smear showed the male pattern. In this case it was recommended that the parents should continue to raise the child as a female in view of their prior acceptance of this sex and the fact that the phallus would probably never develop as an adequate penis. It may be necessary to advise amputation of this enlarged organ at a later date and it is believed that by such means, as well as by the institution of appropriate hormone therapy, the child can develop to relatively normal womanhood although she will remain infertile. Abdominal exploration was performed and revealed the presence of a left testicular structure associated



Fig. 11. Case vi. Indeterminate sex. Chromatin sex negative (male).



Fig. 12. Case vii. Indeterminate sex. Chromatin sex positive (female).

with a right ovarian-like organ. A uterus was present. The testicular organ was removed but the right ovarian-like appendage was allowed to remain intact. The possibility of fertility in this apparent true hermaphrodite would be unlikely in the light of our present knowledge.

CASE VII. Indeterminate sex (Fig. 12): A. L., age one year, was presented as a boy with inadequate development of the genitalia. Examination confirmed the fact that there was a very small penis-like structure and a scrotal area showing underdevelopment without redundancy. There were no demonstrable scrotal contents. The 17-ketosteroid excretion was normal (1 to 2 mg. per twenty-four hours). The blood smear showed the female pattern ("drumsticks" on the leukocyte nuclei). In this case the parents were receptive to the idea that the child was and should be raised as a female especially when it was explained that it would be impossible to achieve either male gametes or a functioning penis. There is, furthermore, the possibility that ovaries are present but more detailed study will be deferred until the time when plastic surgery is under consideration.

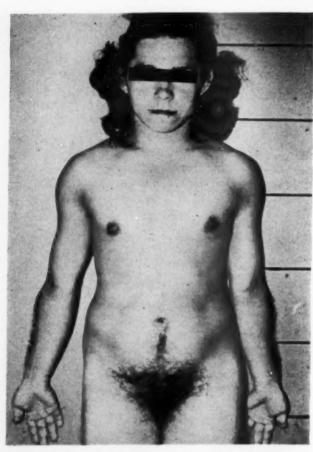


Fig. 13. Case viii. Adrenogenital syndrome. Chromatin sex positive (female).

CASE VIII. Adrenogenital syndrome (Fig. 13): G. R., age nineteen, was a short, hirsute woman of masculine appearance, of Puerto Rican origin, who had never menstruated. She had flat breasts and had always been painfully aware of her appearance. There is no question that it had been the source of perpetual embarrassment to her in her home village. She had undergone amputation of an enlarged clitoris at a very young age in Puerto Rico but the rest of the external genitalia were small. On the basis of the clinical and laboratory data the diagnosis of adrenogenital syndrome was made and she was given the usual corticoid therapy. Treatment was successful, for her previously elevated 17-ketosteroid excretion (80 to 90 mg. per twenty-four hours) fell to normal levels, she began to menstruate regularly, breast growth occurred and apparently ovulatory cycles appeared as judged by her basal body temperature chart and the presence of dysmenorrhea. Despite the masculine features of this patient, the chromatin sex was positive as in all normal women. Had this information been available earlier in her life it would have been extremely valuable to a physician managing her case. It would have emphasized that she was female and she could have been spared much of the mental anguish and uncertainty from which she had suffered before she

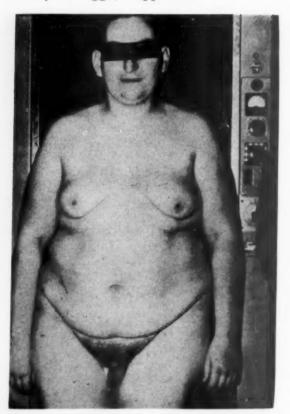


Fig. 14. Case ix. Klinefelter's syndrome. Chromatin sex negative (male).

experienced the irrefutable proof of feminity furnished by her first menstrual period. It would also have provided a useful guide to the earlier institution of hormone therapy.

CASE IX. Klinefelter's syndrome (Fig. 14): R. H., a twenty-five year old white male, was examined in the hospital where he complained of impotence. There was pronounced gynecomastia for which bilateral mastectomy had been performed. He had never shaved and the escutcheon was of the female type. Laboratory examination showed a 17-ketosteroid excretion of 12.5 mg. per twenty-four hours; folliclestimulating hormone excretion was normal. The glucose tolerance test, using an oral dose of 100 gm. of glucose, showed a relatively flat curve. A testicular biopsy specimen (Fig. 15) revealed peritubular fibrosis and hyalinization of the tubular content associated with azoospermia. A biopsy specimen of the breast (Fig. 16) showed duct and glandular hyperplasia of the type usually seen in the adolescent female. The patient was given testosterone therapy by pellet implantation, after which he was able to achieve sexual intercourse which had previously been impossible. The chromatin sex was male (negative).

CASE x. Indeterminate sex (Fig. 17): L. B., a rather attractive two and one-half year old girl, presented with an enlarged clitoris with a small opening beneath

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Fig. 15. Case IX. Testicular biopsy specimen. Peritubular fibrosis. Hyalinization of tubular content. Azoospermia.

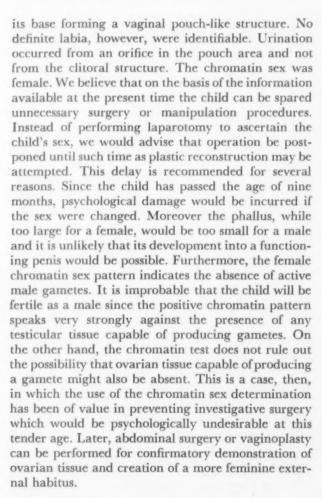




Fig. 16. Case ix. Biopsy specimen of the breast. The duct and glandular hyperplasia resemble that seen in an adolescent female.

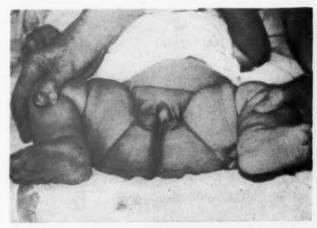


Fig. 17. Case x. Indeterminate sex. Chromatin sex positive (female).

CASE XI. Klinefelter's syndrome (Fig. 18): C. H. was a sixty-seven year old veteran who was admitted to Bellevue Hospital for treatment of congestive heart failure. Physical examination showed moderate gynecomastia and underdevelopment of the testes with a penis of normal size. The patient had been married and was able to achieve sexual intercourse although he had never had children. He had served in the army during World War I. There was a conspicuous absence of body hair but the voice was that of the male. His height was 70 inches (175 cm.) and his weight 165 pounds (75 kg.) Laboratory examination showed a 17-ketosteroid excretion of 8.6 mg. per twenty-four hours. The urinary gonadotrophic hor-



Fig. 18. Case xi. Klinefelter's syndrome. Chromatin sexpositive (female).

mone output was 13.4 mouse units per twenty-four hours. A biopsy of the testis (Fig. 19) revealed a picture identical with that in Case IX characterized by hyalinization of the tubules associated with azoospermia and peritubular fibrosis. The results of the blood smear on the other hand were the opposite of those obtained in Case IX, for here they showed the female pattern (chromatin positive).

#### COMMENTS

These eleven examples have been selected because they well illustrate the type of information we are seeking and the way in which it may be used. In every case, except Cases III and IX, examination of the neutrophils has contributed substantially to the diagnosis.

In Cases I, II, v, vI and XI the test indicates infertility and for this reason is a valuable laboratory procedure. It will be noted that these five patients are living as members of the sex opposite to the indications of their nuclear chromatin but that in every instance the sex that the patient actually adopted gives the best chance of a happy life. From a consideration of Cases IV, VI, VII, VIII and X, however, it can be seen how the



Fig. 19. Case XI. Testicular biopsy specimen. Peritubular fibrosis. Hyalinization of tubular content. Azoospermia.

chromatin smear may be used in helping to determine the sex by which an individual should be advised to live, and contributes to the understanding of the pathogenesis of various conditions.

Gonadal Aplasia in a Male. The patient in Case 1 is remarkable in that, although his cells are female in type, he thinks of himself as a man and is happily adapted to his environment. His wife has had three children by artificial insemination from a donor and the patient has no difficulty in fulfilling the social and emotional roles of father and husband in the family. There is no suggestion that he is at any grave psychological disadvantage as the consequence of his feminine features and there is no history of homosexuality. Care has been taken not to acquaint the patient with the results of the chromatin sex. In his case the finding of the female pattern is probably an unmistakable indication of his infertility. Beyond this, we must admit that we are at a loss to explain the pathogenesis of the syndrome he presents.

Gonadal Dysgenesis. "Gonadal dysgenesis" is the name suggested by Wilkins [11] as a replace-

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ment for the original title of "ovarian agenesis" or "Turner's syndrome." It is exemplified in Cases II and III. Typically, the patient, who has always been regarded as a girl, presents at the endocrine clinic with the history, that although she has reached the age of puberty, her external physical features remain sexually immature or infantile and menstruation has not begun. She may or may not show the additional features of neck-webbing, increased carrying angle of the elbows and coarctation of the aorta. The essential lesion is the absence of the gonad. On this account no clinical response will follow exogenous administration of pituitary gonadotrophic hormones since there is no gonad capable of responding. Indeed, the endogenous folliclestimulating hormone output invariably is already elevated, implying ovarian insufficiency. Administration of ovarian hormones, however, is followed by full development of the external physical features of a woman, for the secondary sex end-organs are readily responsive to the ovarian hormones of which they have been deprived. There is no evidence to suggest that the chromatin-positive and chromatin-negative patients in any way differ from one another in their response to therapy with the sex steroids. Both of the patients in Case II (chromatinnegative) and Case III (chromatin-positive) responded well to replacement therapy.

These two patients are clinically similar even though their chromatin patterns are diametrically opposed. Indeed, when all twenty-three cases of gonadal dysgenesis which we have recently studied are reviewed, we are unable to find any other clinicopathological distinction which accords with the division of these patients into the two groups indicated by their chromatin

With regard to the practical management in Cases II and III it should be said at first that both patients are unquestionably women. In Case II, at least, the patient should never be told of the results of these tests. Both patients have had the usual upbringing of the normal American woman and there would never have been any justification for attempting to consider the patient in Case II as a man at any stage of life, irrespective of any laboratory findings.

In both cases the sex chromatin test has provided useful information. Laparotomy, sometimes recommended for the study of this syndrome, would be pointless in Case II although possibly of some value in Case III. As regards

fertility, all the information presently available leaves practically no doubt that in Case II ovulation and conception can be said to be impossible; this on the basis of the blood smear alone. In Case III information in addition to that provided by the sex chromatin test would be required to reach a similar conclusion.

In Case II the diagnosis can be made on the basis of the blood smear. In Case III there is an increased incidence of "drumsticks" on the nuclei of the neutrophil polymorphs. Our present studies of normal and abnormal women are designed to throw further light on the significance of the frequency of the "drumsticks."

Early diagnosis of gonadal dysgenesis is important from the therapeutic standpoint. Institution of replacement therapy early in life may adequately prevent certain undesirable side effects that are observed as a result of the failure of development of secondary sex characteristics. In addition to the psychological benefits of early replacement therapy, which is usually followed by development of secondary sex characteristics, one also gains two other definite advantages. (1) The patient is able to accept conjugal relationships and enjoy marital partnership. (2) The administration of steroid hormones will prevent some of the degenerative or aging processes that may be seen in these patients (in particular crinkling and vellowing of the skin) so that while in general they may look younger, soon they appear somewhat older than their stated age.

These considerations raise numerous arguments with regard to etiology. Grumbach et al. [11], citing certain animal studies, suggest that the syndrome is due to intrauterine failure of the embryonic gonad and postulate that the further development of the embryo proceeds along female lines because of an intrauterine climate which favors feminity in the absence of the counteracting fetal gonad. This theory does not satisfy us. We believe that the developmental mechanisms are infinitely more complex than is at present understood. In certain cases of primary testicular hypoplasia, as will be discussed, there is also a failure of the fetal gonad but the patient lives as a physical male. Here the intrauterine climate would appear to have permitted fetal development along masculine lines. Furthermore, no hypothesis is available to explain the etiology of the syndrome seen in our Case 1.

Klinefelter's Syndrome. Klinefelter's syndrome, or primary testicular hypoplasia, is in some ways

comparable to gonodal dysgenesis. The patient is born with a gonad which, although it may produce a sex hormone, is incapable of producing a gamete. It happened that the first four patients with this condition whom we examined by the sex chromatin test, including the patient in Case IV, showed the male pattern. Since then, a number of patients, including those in Cases v and xi, have shown a female sex chromatin pattern despite the fact that they have the external genital appearance of the male and have clinical and laboratory findings identical with those obtained in the four patients with a negative chromatin pattern. (Dr. James T. Bradbury of the State University of Iowa sent us blood smears from three such patients, in all of which objective examination showed the female pattern.) Similar findings have been reported by other workers [14,15]. Gynecomastia may or may not be present but there invariably is a scrotum with definitive scrotal contents, a penis that may be normal, and a male-like habitus and psychological make-up. Histologically, the testes are characterized by peritubular fibrosis, hyalinization of the tubular contents and a normal number of Leydig cells. We believe that the finding of a chromatin pattern of the female type makes the prognosis with respect to fertility hopeless, for it indicates that the gonads are incapable of producing gametes. These patients, while comparable to the woman with gonadal dysgenesis in that they lack the ability to produce a gamete, differ in one important respect: in Klinefelter's syndrome there is a gonad of definite structure, with cells which produce androgenic substances. While replacement therapy is not as important here as it is in the female, it may be necessary to inform the patient that he will never be able to procreate and that replacement therapy may eventually become necessary to overcome the inability to achieve orgasm, or to increase diminished potentia when present. We have also found this test to be of value in detecting Klinefelter's syndrome earlier than might otherwise be possible, as for example in Case v. While there was a disproportion between testicular and penile size, which suggested the syndrome, the chromatin pattern made the diagnosis more likely in view of the absence of gynecomastia.

Another remarkable fact has come to light in the examination of blood smears of patients with Klinefelter's syndrome. We have reported [10] that in several patients with this disease the

number of neutrophils which have "drumsticks" is very much less than in normal women. Plunkett and Barr [16] have recently encountered the same situation in Klinefelter's syndrome. This reduction in the number of "drumsticks" has been a matter of provocative interest to us but an authoritative statement must await the results of fuller studies of normal women.

Adrenogenital Syndrome. The sex chromatin test may be of inestimable value in the diagnosis of adrenogenital syndrome or at least may lead to suspicion of its presence. This is particularly true in the newborn child with a scrotal-like structure, a larger penis than one would normally expect, and hypospadias. If there is sure clinical evidence of adrenal cortical insufficiency, such as anorexia, vomiting, weakness and leukocytosis, the diagnosis of adrenogenital syndrome is likely, especially if the chromatin sex pattern is female. In our opinion, such babies probably are pseudohermaphrodites in whom congenital adrenocortical hyperplasia occurred in utero, with excessive endogenous androgen production resulting in the development of the Wolffian anlage and either indifferent external genitalia or more definitive masculine organs. The diagnosis can be confirmed by determination of the urinary 17-ketosteroid output. The presence of the female chromatin sex pattern would then indicate that such subjects are anatomical females with the physiologic expression of overproduction of androgens.

The chromatin sex pattern is of great help in the management of females with a markedly enlarged clitoris and indefinite vulvar development in whom the 17-ketosteroid excretion is increased. If the 17-ketosteroid excretion is not included in the study of these children the diagnosis may be missed, but the finding of the female sex chromatin pattern in a child with partially female external genitalia and a markedly enlarged clitoris should strongly suggest congenital adrenocortical hyperplasia. Corticoids should be administered early to suppress excessive androgen production by the adrenal cortex. By the use of adequate corticoid therapy, precocious sexual maturity will be prevented and a normal menarche will be achieved. Properly treated, these patients may be expected to ovulate and may eventually bear children. Ovulation has finally taken place in Case vIII. The determination of chromatin sex, if conducted earlier in life, would have been

instrumental in achieving a better psychological adjustment. Early institution of corticoid therapy has the added advantage of preventing premature closure of the epiphyses occurring in these patients as a consequence of increased elaboration of sex steroids from the adrenal. Such therapy will prevent the short stature that patients with congenital adrenal hyperplasia usually present and permit more normal growth.

In Case IV, knowledge of the chromatin sex in a fourteen day old child, together with the elevated 17-ketosteroid excretion, lessens the need for abdominal exploration, as does also the good response to corticoids. Assurance may be given to the parents that in all probability their infant has ovaries capable of functioning and that with proper therapy and surgery one can anticipate a functioning female who is normal both reproductively and sexually. Cases of this type are seen from time to time in which, for lack of information concerning the chromatin sex, exploratory surgery has been performed; indeed in some instances we have seen an attempt made to transpose "abdominal testes" into the scrotum.

Sexing of Infants. Since society recognizes only male and female, the physician may be called upon to advise which sex is more desirable for the patient to adopt. This is an individual problem, to be studied on its own special merits, with due regard to the physical attributes of the patient, the attitude of the parents and the mores of the society in which they live. Often, as in gonadal failure, the problem may resolve itself into a choice between impotent masculinity and infertile feminity, and the decision must rest partly on philosophical considerations which transcend the limitations of morphological data. The status of the neuter individual in a community, never a completely happy one, can be made more tolerable only by a consideration of all the aspects of sexuality in relationship to environment.

In choosing the sex to which an individual should belong, it is a mistake to place too much emphasis upon one aspect or category of sex. Certain features, however, may be over-riding, e.g., (1) virtual absence of phallic organ, (2) an already established psychological orientation, and (3) intransigence on the part of the parents.

Children have been seen with predominantly female external genitalia but with the chromatin sex pattern of the male. However, on the basis of a small penis or a large clitoris, we have often

believed that the chromatin sex pattern should not be allowed to guide too completely the future management of the patient. Here the clinical judgment of the physician with respect to the potential functioning of the phallus must play as great a part as any other consideration in determining which sex should be advised. In other words, a chromatin male with a small, infantile or ineffectual phallus would be incapable of performing sexually as a male, while the same individual brought up as a female and equipped with a vaginal pouch by plastic surgery could learn to live a normal marital life. However, the problem of infertility remains unchanged whether the child is brought up as a male or as a female. In addition, the presence of a small phallus in a child or infant with a female chromatin pattern but indeterminate sex who has been named as a girl can be spared the necessity of a Japarotomy until the time when proper development of the tissues has occurred to

permit vaginoplasty to be initiated.

The importance of the chromatin sex may be emphasized, in retrospect, by the case recently presented by Arneaud et al. [17]. The patient, a true hermaphrodite aged eighteen, brought up as a male, possessed some of the external genital features of the male and some of the female. At puberty, monthly bleeding episodes occurred from a small orifice posterior to the penile structure. Laparotomy revealed a uterus, a left testis, and left and right ovaries. Corpora lutea were present on both sides. Despite these findings, hysterectomy and orchidectomy were performed, the external genitalia of the male were accentuated, and both breasts were amputated. The patient now feels himself to be a male and treatment is regarded as successful. In this tragic case little else could have been done in view of the age and social circumstances. However, with a knowledge of the chromatin sex, perhaps the birthright of this individual to procreate could have been preserved if the female social sex had been chosen instead of the change into a male. The patient was a woman in all respects with the exception of psychological orientation, large size of penis, smallness of vagina and presence of non-functioning testicular tissue. The operation performed constituted castration and removal of all powers of procreation. If in infancy it had been established that the child was chromatin-positive, a different course could have been planned. Brought up as a male, the patient would inevitably be sterile;

if the female sex had been chosen one would have every reason to expect that fertility would have been possible. (This is confirmed by the presence of a uterus, tubes and oviduct associated with ovaries capable of producing active corpora lutea.) In this way, knowledge of the chromatin sex would have assisted in choosing the sex and in directing surgical and therapeutic management.

#### SUMMARY

The subject of chromosomal sex is discussed and its great importance in diagnosis is illustrated by the presentation of eleven cases.

Investigation of the patient's chromatin sex has become an indispensable clinical procedure for the study of intersex, in planning the endocrinological rehabilitation of the sexually disabled, and in evaluation of the reproductive prognosis of infants.

Acknowledgments: Patient L. B. (Case x) is from the Endocrine Clinic of the Newark Beth Israel Hospital. We are indebted to Dr. Willard Allen of Washington School of Medicine, St. Louis, Missouri for the operative findings in patient M. C. (Case vi).

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# Physical Therapeutic Measures in the Treatment of Chronic Bronchopulmonary Disorders\*

Methods for Breathing Training

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Breathing difficulty in chronic bronchopul-monary disease results principally from mechanical disturbances of the respiratory apparatus which only partially can be corrected by drug therapy. Thus, certain physical measures are important in the effective treatment of such disorders as chronic obstructive bronchitis, bronchiectasis and bronchial asthma, which are the conditions most frequently associated with chronic pulmonary emphysema. European workers [1-6] prior to 1935 frequently had suggested physical therapy as an adjunct to the treatment of asthma, emphysema and other chronic bronchopulmonary disorders. Thomas [7], as well as Cournand and associates [8], as early as 1936 discussed in the American literature the necessity for a physical approach to the disordered breathing of patients with chronic dyspnea. Since that time, many descriptive reports have appeared presenting certain aspects of the technics of physical therapy, as well as some clinical and physiological evaluations [9-27].

It is the purpose of this report to discuss the physiological basis and details of the use of certain physical measures of value in the treatment of chronic bronchopulmonary disease. A physiological evaluation of these methods was presented previously [28].

## BASIS FOR BREATHING TRAINING

A common denominator of these conditions is expiratory difficulty which results either in airtrapping in the lungs or in an increased amount of time and effort being spent during expiration. Under conditions of rest, this frequently is not

such a serious problem, but with exertion, increased ventilation leads to more air-trapping and over-distention of alveolar sacs. Overdistention, in turn, initiates an increased number of afferent reflexes from the lungs which induces further increases in ventilatory effort and frequently the symptom, dyspnea. Figure 1 is an example of some of the consequences of increased ventilatory effort in a patient with asthmatic bronchitis. Progressive air-trapping is noted by a rise in the respiratory mid-position either during voluntary hyperpnea or in the course of increased ventilation resulting from exercise. The trapped air results in a serious increase in the work of breathing as well as in an increase in functional residual capacity with decreased alveolar ventilation, owing to excessive dilution of each tidal breath. Similar changes in ventilatory pattern are occasionally noted when patients with asthma or emphysema become apprehensive during the spirographic studies. Such increased ventilatory effort with air-trapping may cause the patient to request that the test be terminated. In most instances, reassuring the patient and encouraging him to breathe slowly and to concentrate on expiration will help to restore his respiratory mid-position to the previous lower level with resultant relief of the respiratory symptoms. It is quite apparent clinically that many attacks of asthmatic type dyspnea are precipitated by such a mechanism in patients with pulmonary emphysema. Moreover, coughing attacks almost invariably cause similar air-trapping in patients with chronic obstructive pulmonary disorders, unless the patients can be

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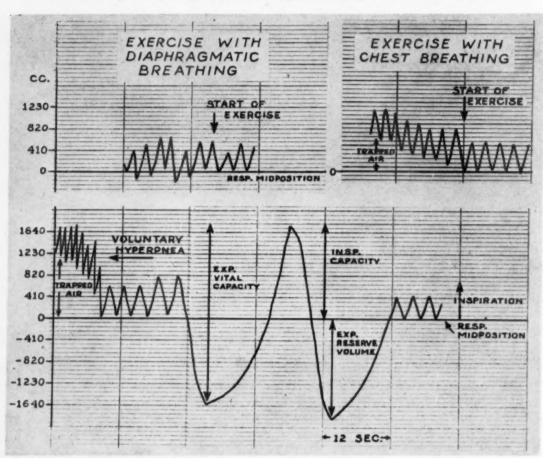


Fig. 1. The effects of increased ventilatory effort in a patient with severe asthmatic bronchitis and pulmonary emphysema. The top two tracings show the air-trapping and rise of the mid-position which occur with chest type breathing but which are prevented with abdominal-diaphragmatic breathing. The bottom tracing shows the relation of the breathing pattern during voluntary hyperpnea, with chest breathing, to the quiet breathing pattern and the rest of the dynamic lung volumes.

educated to give some attention to the avoidance of successive deep inspiratory efforts accompanied by forceful expirations. When air-trapping and over-distention occur during attempts to evacuate secretions by coughing, evacuation is impaired since the effectiveness of a cough is dependent upon the maintenance of a high velocity of expiratory air flow, a maneuver which patients with chronic pulmonary emphysema cannot successfully achieve because of a "check valve" type of obstruction with air-trapping which has been described by Dayman [29], who has shown the obstruction to be a result of a premature expiratory collapse of airways owing to decreased elastic forces supporting the airways.

In addition, air-trapping and over-distention increase the work of breathing both by causing the lung to be distended more nearly to its elastic limit, where much greater pressure differential is required to maintain adequate ventilation [30-32], and also by increasing the resistive work. The mechanism of increased resistive work with air trapping is not clear, but may be due to reflex bronchospasm or compression of airways by over-expanded segments.

Moreover, such over-distention probably plays an important role in the pathogenesis of emphysema as described by Heckscher [33] in an exhaustive treatise on the clinical manifestations of the disease.

Since the prevention of air-trapping is important to patients with chronic obstructive pulmonary disorders, measures directed toward the prevention and alleviation of over-distention are clearly indicated.

Finally, asynergia and disorganization of respiratory muscular function resulting in an increased effort of breathing as observed in chronically dyspneic and anoxic patients has

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been described in great detail by Cournand and associates [8]. Remarkable improvement in respiratory function was noted in their patients after a period of breathing training exercises.

#### AIMS OF BREATHING TRAINING PROGRAM

The over-all aims of the physical approach to the treatment of chronic bronchopulmonary disorders are summarized as follows:

(1) To educate the patient as to the nature of his disease and to the necessity for altering his breathing habits.

(2) To achieve a more effective alleviation of dyspnea by teaching the patient to suppress the strong natural desire to relieve his shortness of breath by hurried gasping inspiratory efforts which only result in over-inflation of the lungs and further air-trapping, as well as disproportionate increase in the work of breathing.

(3) To improve effective alveolar ventilation at least insofar as is possible depending on the limits imposed by the intrinsic disease of the lungs.

(4) To correct over-distention of the air spaces which may have serious adverse effects on the lungs if such over-distention is continued for prolonged periods of time.

(5) To effectively decrease the work of breathing in order to minimize the ventilatory requirement for any level of metabolic carbon dioxide production.

(6) To improve the effectiveness of the cough mechanism in order to obtain better clearing of retained bronchial secretions, since the retention of secretions not only causes further obstructive ventilatory insufficiency but also increases the tendency for frequent and recurrent bronchopulmonary infection.

(7) To increase the effectiveness of nebulization therapy by emphasizing preliminary exhalation of trapped air, combined with a slow, relaxed inspiration followed by a one to three second pause [34].

(8) To alleviate tension and apprehension through instruction in muscular relaxation and coordination and, further, to provide the patient with a reassuring sense of security that will make him a better match for the terrifying dyspnea which has captivated him.

(9) To improve activity tolerance and relieve exertional dyspnea through instruction in the coordination of an abdominal-diaphragmatic pattern of breathing with other physical activity.

In regard to the use of the term "diaphragmatic breathing," direct voluntary control of the diaphragm does not occur as a consequence of training [35]. However, proper control of the abdominal and lower thoracic muscles causes the diaphragm to be moved upward and the chest cage downward. With this type of training, the loss of elastic forces in the lung and the thorax can be replaced in part at least by active abdominal muscles. If the diaphragm can be further restored to a more normal elevated relaxed position, it can then achieve a greater downward excursion during contraction and thus become a more effective natural inspiratory force.

## METHOD OF TRAINING

Preliminary Evaluation of Patients. Assessment of the nature of the disordered respiratory activity and of the extent of disability is a necessary preliminary step. Such evaluation can best be achieved by functional chest fluoroscopy [36], physical measurements of the respiratory apparatus with the technics of Newman [37] and Rodholm [38] and, finally, by a battery of pulmonary function tests.

Studies designed to measure activity tolerance, the work of breathing, and gas exchange are of particular importance, since ventilatory capacity measurements alone often do not display significant improvement when the patients have been benefited as judged by subjective evaluation as well as by measures more closely related to gas exchange or the work of breathing.

These examinations help to provide an understanding of what aspects of the abnormal breathing pattern will require the most correction, and also provide an objective means of following the progress of the patient.

Education—Relaxation. At the same time the pre-treatment evaluation is being accomplished, education of the patient in regard to the nature of his disease and to the need for correction of his breathing pattern can proceed.

For the most part, patients with chronic bronchopulmonary disease and emphysema will complain of a "tightness" in their chests and the inability to "draw a long breath" or inability to get a breath deep into their chests. Such patients rarely appreciate that these sensations stem from the fact that their lungs are over-distended and virtually full to capacity with air that is poorly exchanged. Voluntary hyperpnea should be inflicted on the patient in order to demonstrate that deep fast breathing does not alleviate dysp-

nea for him but increases it. Likewise, the difference between a rigid, braced inspiratory position while sitting, standing or walking and a more comfortable, relaxed, "forward bending" position [15] should be demonstrated to the patient in order to emphasize the inefficient energy expenditure effected by the former attitude.

The initial approach to teaching muscular relaxation is made simultaneously with the previously mentioned steps. The technics for teaching relaxation are best individualized both for the patient and for the physician or therapist. However, in general, the methods of Fink [39] or Jacobson [40], either separately or in combination, have been used effectively. It must be emphasized that muscular relaxation is a prerequisite to any type of successful muscle retraining. Moreover, muscular relaxation conserves energy for more useful functions.

Whereas every aspect of the diaphragmatic training must be presented and discussed here as if each were a separate step in the training procedure, most of the functions are conducted almost simultaneously. This is particularly true of the preliminary training and education phase, which should be conducted in conjunction with initial diaphragmatic training. The precise manner of proceeding with the training must also be individualized for each patient, depending upon the following factors: (1) the nature of the underlying disease; (2) the extent of the physiological disturbance induced by the disease as well as the physical disability accompanying the physiological alterations; (3) the extent of emotional maladjustment that is either intrinsic to the patient or is a result of the disease from which he is suffering; (4) the facility with which the patient can understand and execute the instructions from the outset of the treatment; and (5) finally, and frequently most important, the nature of the interpersonal relationship between the therapist and the patient. The qualifications of the therapist are a matter of considerable importance. Livingstone [18] has appropriately indicated that the therapist should be " . . . an amiable individual with much personal enthusiasm and one who has strong convictions in regard to the value of the treatment, based on an ample experience and detailed knowledge of the techniques."

In every instance, individual training periods should be preceded by bronchodilator therapy when such therapy is otherwise indicated in the treatment of the patient's pulmonary disorder. In certain cases, oxygen inhalation by mask or catheter or intermittent positive pressure breathing will be indicated either for the purpose of obtaining preliminary relaxation or for the purpose of maintaining optimal relaxation and cooperation during the treatment period. Nebulization of bronchodilator drugs is conducted by the method of slow, complete exhalation, preceding a slow, full inspiration, and followed by a momentary pause as described previously by the author [34]. This method is based on the same physiological principles as is the entire breathing training program.

Quiet Abdominal-Diaphragmatic Breathing. In most instances, the patient is placed either supine or in a 20 to 30 degree head-down position with an 8 to 10 pound sand bag on the lower midabdomen. It is well to have the patient place one hand on the upper part of his chest to help remind him not to use his chest during inspiration. His dominant hand should, at the same time, be placed over the upper part of his abdomen to call attention to the inward motion that should occur during expiration and the outward motion that should occur during inspiration. It is very useful in many patients to explain this basic maneuver by the use of the phrase, "Blow the air out through your chest and breathe down into your belly." It is important to start the maneuver with expiration either through the nose or, better, through pursed lips, making the sound of "f" or "s." Inspiration should always be performed slowly through the nose. Not infrequently, considerable reassurance and encouragement is necessary to accomplish a supine position for these patients even before a head-down attitude can be attempted. Every effort possible must be made to insure the patient's comfort. In patients with severe kyphosis, achievement of a relaxed head-down or supine position may be virtually impossible. However, in most instances, if enough trouble is taken with the aid of pillows and pads, the subjects can be made comfortable. In certain cases, a program of postural drainage to promote bronchial toilet must precede attempts to start breathing training since frequently coughing and expectoration will make it difficult for the patient to relax and concentrate on the breathing routine. In such persons, the head-down position may produce a choking sensation. These objections usually can be overcome by reassuring the patient that this choking sensation is due to the secretions which are draining into the larger bronchi. The

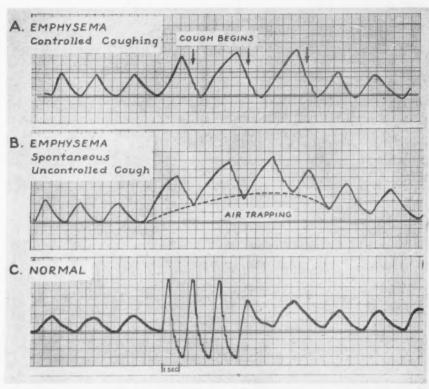


Fig. 2. The effects of controlled coughing (A) as compared to spontaneous uncontrolled coughing (B) in a patient with asthmatic bronchitis and chronic pulmonary emphysema reveal that when partial expiration is performed before the cough begins (A), air trapping is prevented and more complete emptying of the lungs is accomplished. For further comparison, a tracing of three coughing efforts produced by a normal person are shown (C). This figure further illustrates the inability of such severely obstructed patients to effect a significantly greater velocity of air flow during the expiratory phase of the cough when initiated from a level of greater lung expansion (B) as compared to a level of lesser lung expansion (A).

draining secretions initiate coughing and cause increased large airway obstruction by virtue of the fact that the material which was previously lodged in segmental bronchi has moved up into the proximal airways. Effective evacuation of such obstructing secretions will be accompanied by improved breathing. Persistence must be practiced. Except in those situations in which secretions are very loose and otherwise easily evacuated, the drainage process is slow and sometimes discomforting. Utilization of intermittent inspiratory positive pressure breathing (IPPB) with nebulized wetting agents, and bronchodilators may be helpful in making it possible to continue the head-down position in such patients. In this regard, we have found that most patients will remove the mask or mouthpiece of the pressure breathing apparatus with the onset of a coughing paroxysm. Patients should be informed that it is not necessary to remove the mask or mouthpiece, since coughing is more easily and more effectively performed with the aid of the intermittent positive pressure breathing device, particularly if higher pressures (20 to 40 cm. of water) are used for this purpose. The patients should remove the mask or mouthpiece only when the secretions have been raised into the throat where they can be easily expectorated. This manner of employing the intermittent positive pressure breathing device during postural drainage and coughing relieves anoxia and helps to prevent bronchospasm which occurs almost invariably during severe paroxysms of coughing in many patients. Furthermore, it is possible for the anoxic patient to utilize more effectively a controlled type of coughing while breathing oxygen.

Figure 2 illustrates the difference between controlled (A) and spontaneous (B) coughing in such patients. This is compared with the respiratory pattern of a normal subject (C) during spontaneous coughing. The manner in which airtrapping is minimized is illustrated in the example of controlled coughing. The patient is instructed to exhale partially, then to make short expiratory bursts during the latter part of the

expiratory phase and subsequently avoid a maximal inspiratory effort. Even though gasping deep inspirations are quite natural during coughing in the normal subject (C), such efforts invariably lead to air-trapping in the patient with obstructive ventilatory insufficiency, as is illustrated by a failure to recover to the pulmonary mid-position during the expiratory phase of the cough in the respirographic tracing of uncontrolled coughing. Moreover, the intense effort that goes into a frantic cough only tends to make the cough less effective in the evacuation of secretions since the sudden large increases in intrathoracic pressure cause collapse of the airways in the manner described by Dayman [29] and others [32].

The head-down position previously described will result almost invariably in some increase in abdominal and diaphragmatic excursion within a matter of moments after the posture is assumed by a properly relaxed patient. That the increased abdominal breathing under these circumstances represents greater diaphragmatic excursion has been repeatedly confirmed by comparative fluoroscopic observation of the diaphragm before and after the patient assumes the head-down position. The correlations between diaphragmatic excursion and tidal ventilation in various bodily attitudes have been graphically recorded by Wade and Gilson [41]. Moreover, studies by Barach [42] as well as repeated observations in our own laboratory have shown improved ventilatory function resulting from the use of the head-down position as a means of inducing a slow, relaxed abdominal-diaphragmatic type of breathing in most patients with chronic pulmonary emphysema. Occasionally, the head-down position will cause nasal congestion and obstruction which can usually be controlled by judicious use of a small amount of thenylephrin hydrochloride, 1/4 per cent, administered just before the patient lies down. A pillow may be permitted under the head but not under the shoulders.

Once the patient has successfully accomplished a relaxed head-down position, he is asked to focus his attention first on the expiratory phase of respiration, in order to obtain optimal emptying of his over-distended lung and at the same time to minimize attention being given to inspiration, until the desire to utilize thoracic muscles of inspiration is overcome. Subsequently, some attention should be given to directing inspiration to the abdomen, thus caus-

ing protrusion of the abdominal wall. A pattern of emphasis on expiration constitutes in part a reversal in respiratory sequence for the asthmatic or emphysematous patient who has been continuously making exaggerated thoracic inspiratory efforts in order to relieve his dyspnea. It has been suggested [23] recently that attempts to achieve expiratory dominance of the respiratory rhythm are awkward and generally ineffective. Indeed, it is not the normal rhythm of respiration but, again, if air-trapping is to be prevented in these patients, the importance of emptying the lungs adequately before each inspiration must be impressed in some manner. The methods described have been most effective for this purpose in our hands. The significance of this is particularly apparent when the patient leaves the head-down or supine position to assume the more erect postures, whereupon expiration is no longer adequately or subconsciously performed in most instances until after many months of training.

Pursed Lip Breathing. The value of pursed lip expiration or the equivalent thereof has been questioned by some who propose that the mouth should be left open and no additional resistance to expiratory flow be introduced [23]. There are considerations in support of either view. On the one hand, since expiratory obstruction to air flow is a basic problem in asthma or emphysema, it might seem reasonable to object to any maneuver which would further increase resistance to air flow. On the other hand, the most important mechanism of obstruction in pulmonary emphysema is a premature collapse of the airways owing to the large difference between the higher intrapleural space pressure and the lower intrabronchial space pressure during the expiratory phase [29,32]. This pressure difference is largely a result of the diminution in elastic forces which tend to support the airways. Pursed lip breathing, by causing obstruction above the bronchial level, produces an increase in intraairway pressure in order to reduce the effective transbronchial pressure difference, thus decreasing the tendency for premature collapse of the airways. The net result is a more complete emptying of the lungs so that the patient can breathe at a lower pulmonary mid-position with a smaller functional residual capacity.

We have found that pursed lip breathing is very helpful for those patients in whom early expiratory collapse of the small airways presents a significant impedance during forceful expiratory efforts. Such early collapse of the airways is evidenced by a sharp deviation of the rapid expiratory volume curve away from the ideal exponential-type emptying curve early in the expiratory phase indicating an abrupt decrease in the rate of air flow. Similar abrupt reductions in air flow were demonstrated by Dayman [29], with direct pneumotachographic flow tracings. This abrupt change in expiratory flow occurs when intrathoracic pressure exceeds intrabronchial pressure plus the elastic forces which maintain the airways.

Decompression and Abbreviated Diaphragmatic Breathing. Once the patient has mastered control of abdominal type respirations, after the fashion described herein, efforts can be made to obtain contraction of the lower thoracic cage during expiration as well as the upper part of the abdomen in order to achieve more complete expiratory emptying of the lungs. This is considerably more difficult than most of the other maneuvers and may require many months of training. Compression is achieved by wrapping the arms around the lower part of the chest and assisting expiration by pulling in lower ribs and compressing the upper part of the abdomen, by folding the trunk over on the arms while in the sitting position. This exercise should be performed in a relaxed manner, again with lips pursed during expiration, and inspiration should always be performed slowly through the nose. Barach and co-workers [43] now use a more effective mechanical device for assisting lower thoracic and abdominal expiration. Abbreviated abdominal-diaphragmatic breathing consists essentially of successive quick expiratory efforts directed by the dominant hand. These maneuvers are particularly valuable in accomplishing decompression when increased breathing effort has led to air-trapping and dyspnea, such as may be the case either during an impending asthmatic attack or with exertion. Usually, the evacuation of bronchial secretions is also favorably assisted by these maneuvers.

Activation Program. Quiet, slow abdominaldiaphragmatic breathing should be attempted first in the sitting position, then in the standing position, and finally, must be learned in the walking position and in conjunction with upright working maneuvers. All preliminary training sessions should be conducted by an expert so that flaws in the patient's technic will be quickly corrected lest improper breathing habits become too firmly entrenched. Later the responsibility

for continuation of the training can be transferred to the patient or to other persons concerned with his care. Once the patient is ready to walk with mastery of a diaphragmatic type breathing, it must be reemphasized that all activity should be performed in rhythm with an abdominal pattern of breathing and no attempt should be made to fit the breathing rate or rhythm to the activity. Activity should cease when the patient feels the necessity to interrupt his breathing pattern or if dyspnea becomes otherwise uncontrollable. Exercise tolerance can be very effectively enhanced by permitting the patient to breathe oxygen by nasal catheter during progressively graded activity [25], using the "forward bending" position [15]. Walking or stepping up can be performed as follows: three or four steps can be taken during expiration and one to two steps during inspiration.

An example of how activity has been coordinated with breathing is illustrated by a farmer who, among other things, learned to chop wood by taking two or three strokes with his ax during expiration with a momentary rest or pause in his activity during inspiration. Another example was that of a carpenter who learned to hammer and saw in a similar fashion so that he was able to return to work and get along well except that he could not lift heavy objects or work with his hands overhead without respiratory distress developing because under these circumstances his respiratory apparatus would be in an inspiratory position in which expiration was compromised.

The frequency of training periods and the duration of treatment deserve considerable emphasis. For these patients, successful employment of the methods described herein constitutes literally a new way of life. Obviously only in rare instances can this be accomplished with the average patient in a few or infrequent training periods. Just as it is apparent that the Saturday afternoon golfer rarely achieves striking proficiency in his athletic endeavor, so it is that the patient who hopes to acquire proper breathing habits must practice prodigiously. Wherever possible, supervised training periods should be conducted at least once or twice daily with the patients practicing as frequently as possible, but at least four to six times daily. Any time the patient becomes dyspneic attention should be directed to abdominal-diaphragmatic breathing. Once treatment is started, it should be continued indefinitely.

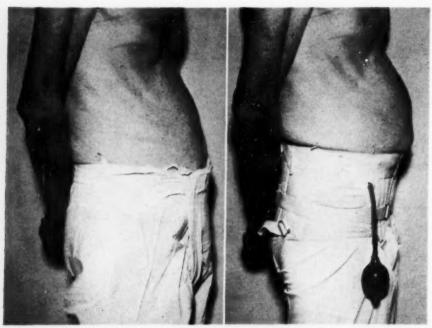


Fig. 3. The left hand portion of this figure illustrates a protuberant, pendulous abdomen in a patient with chronic bronchitis and pulmonary emphysema. This is usually accompanied by marked lowering of the diaphragms and diminished diaphragmatic excursion. When displacement of the abdomen upward results in ascent of the diaphragm and increased diaphragmatic mobility as visualized under the fluoroscope, lower abdominal supports provide improved mechanical function of the respiratory apparatus and often considerable improvement in exercise tolerance since the effects of such a protuberant abdomen are exaggerated in the upright position. The support shown (Camp Model 820) includes an inflatable pad for further compression of the lower part of the abdomen, particularly in thin patients.

# ALLIED PROCEDURES

Abdominal-Diaphragmatic Supports and Pneumoperitoneum. Most middle aged or older persons have considerable relaxation of the abdominal musculature so that some type of abdominal support is usually necessary in order to help maintain the diaphragm in a more normal relaxed elevated position, particularly during upright activity. The Camp type\* emphysema belt (Fig. 3), has been found satisfactory for this purpose. This appliance is available with or without an inflatable pad which provides lower abdominal compression inside the support. The pad is not necessary for patients with obese abdomens, but in thin patients with scaphoid abdomens, there is little with which the depressed diaphragm can be supported unless some such device is employed. Gordon [44] and Barach [15,25] have successfully employed a similar type of belt. † In some instances, simple elastic lower abdominal supports are more comfortably tolerated and are functionally satisfactory. Abdominal supports tend to sup-

\* Available through Camp, Jackson, Michigan.

† The Gordon-Barach Emphysema Belt, available through Spencer, Inc., New Haven, Connecticut.

port the recoil effect of the elastic function of the lungs, aid in the restoration of the diaphragm to a more normal relaxed position in the chest, and also serve a very important role in improving the effectiveness of the cough mechanism. A simple method for testing a patient to determine whether or not an abdominal support will be helpful is to compress the lower part of the abdomen while observing the diaphragms fluoroscopically. If diaphragmatic excursion is increased or the end-expiratory position of the diaphragm is elevated, the patient will usually derive significant benefit from a support. Another helpful maneuver is to apply a support and have the patient execute some walking exercise and note the time of onset of dyspnea. Then, after a rest period, remove the belt and have the patient repeat the exercise to ascertain whether or not the support had increased the exercise tolerance. This maneuver can be repeated to the satisfaction of the observer.

The same role which has just been described for emphysema belts also holds for therapeutic pneumoperitoneum [45–54]. Pneumoperitoneum appears to us to have served this function particularly well in thin patients, in certain in-

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stances more successfully than have emphysema belts. Pneumoperitoneum offers the added advantage that air is compressible and thus inspiration is often easier with abdominal air than with an abdominal belt. Moreover, the air is constantly effective whereas a belt can be taken off. There are three particular situations in which therapeutic pneumoperitoneum has been most helpful: (1) Patients who simply cannot develop control of abdominal or diaphragmatic breathing in spite of prolonged expert training frequently achieve improved diaphragmatic excursion promptly after the institution of pneumoperitoneum. (2) Patients with an acute exacerbation of bronchopulmonary inflammation accompanied by excessive obstructing secretions and an ineffective cough mechanism are frequently in a state of progressive ventilatory insufficiency with carbon dioxide narcosis. However, if pneumoperitoneum is combined with effective bronchodilator therapy and assisted respiration, particularly by the use of intermittent positive pressure breathing devices, dangerous carbon monoxide accumulation frequently can be corrected or prevented when continuous oxygen therapy is indicated for the relief of anoxia. (3) Finally, in those patients with chronic bronchopulmonary infection with copious secretions and again an ineffective cough mechanism, better evacuation of secretions can be achieved with effective pneumoperitoneum therapy, particularly when combined with vigorous continuation of other adjunctive therapy including appropriate antibiotics, bronchodilators and wetting agents. In certain patients with very relaxed abdominal walls, it is necessary to combine a belt with pneumoperitoneum to enhance the effectiveness of the latter. Moreover, in some cases it has been found desirable to use the belt with an inflatable cuff so that as the pneumoperitoneum air is reabsorbed, the effectiveness of the pneumoperitoneum can be maintained by inflating the cuff to an appropriate level until the next refill is

The technic of instituting pneumoperitoneum therapeutically in patients with chronic nontuberculous bronchopulmonary disease has been presented in meticulous detail by Banyai [46]. In addition, the observations by Ricci and Cerulli [52] and later by Beck and associates [53] concerning the venous pressure during pneumoperitoneum are helpful. The therapeutic value of pneumoperitoneum when properly used, in

selected cases, has been repeatedly demonstrated [43-46].

#### ACCESSORY MUSCLE CORRECTION

Frequently, strengthening or relaxing exercises for the shoulder girdle, lower thoracic cage, or abdominal muscles are clearly indicated. When this is the case, most physiotherapists will utilize the technics similar to those reported by the Asthma Research Council of England [3], as well as those described by the Kendalls [55]. These methods have been redescribed by Fein [19,20] and Derango [26]. In younger patients in whom muscles and joints are still mobile, corrective postural exercises should be instituted to prevent progressive cervical kyphosis and lumbar lordosis. However, the so-called "military bearing" is improper in the case of the asthmatic or emphysematous patient because this posture places the respiratory apparatus again in an inspiratory position and compromises expiratory efforts. Breathing is usually mechanically aided by the "forward bending" position during walking, as demonstrated by Barach [15].

General physical activity is an important part of the over-all therapeutic program in order to maintain muscular efficiency. Such activity should be controlled within the limits of what the patients can do without resorting to frantic exaggerated breathing. In some cases, it may be necessary to give the patients oxygen by nasal catheter or mask during ambulation in order to prevent serious hypoxia. This can be accomplished by utilizing long lengths of rubber tubing from the oxygen source to the patient, or small portable oxygen tanks.

#### DISCUSSION ON PHYSIOLOGICAL EVALUATION

In recent years, several papers [56-59] have appeared reporting on the evaluation of breathing training in patients with chronic bronchopulmonary disease. In general these authors have presented skeptical views of breathing training. Several criticisms can be levelled against certain of these studies. Perhaps the most important of these is that the use of statistical averages for the evaluation of therapeutic procedures in a random group of patients with a physiologically quite variable, chronic, and essentially progressive disease is apt to result in either overly pessimistic or optimistic opinions in regard to the value of a method, depending on the particular group of patients studied. In all the reported series, nearly half the treated

patients showed improved ventilatory function; many showed no change. As is obviously the case with any other form of accepted therapy in these disorders, some of the patients show a natural deterioration of ventilatory function. Thus, the importance of any form of therapy that can halt the relentless progression of these disorders should not be condemned as useless simply because the value as assessed by certain objective measures is lost in the average of a series. The aims of these methods must be kept clearly in mind. If the desired effect can be obtained in individual patients, its failure in others should not lead to a refutation of its value in all cases.

The distinct impression is gained from certain of these studies that the training was carried out in a casual manner without adequate education or indoctrination and certainly with training periods too infrequently spaced. In the series reported by Miller [28], the patients in most instances were hospitalized for three or more months continuously during the period of intensive training. The shortest period of training prior to reevaluation was six weeks. In many patients, objective improvement was not achieved for three to six months. These patients had expert supervised training two to four times daily both by the physicians and the chief physiotherapist. Training was carried out either individually or in classes, depending on how the patients progressed and which method was best suited for the individual.

From the comments of some observers, one often gains the impression that these procedures would be condemned as useless if major improvements in the maximal breathing capacity or vital capacity were not demonstrable. Often no major change in such maximal stress tests can be demonstrated when the patients are clearly benefited as evidenced by more effortless breathing at rest and improved mild exercise performance. Much of such improvement is a result of physical conditioning of the patient with improved efficiency of muscular functions including breathing. It is not ordinarily possible to obtain physiological evaluation of such physical conditioning.

Finally, it is important to continue training and to maintain the foregoing principles as an integral part of the therapy even though short term or immediate evaluations do not reveal major functional changes as ascertained by the conventional pulmonary function tests, for the long-term benefits that accrue are proved in a long experience [1-28,60,61] to be of value in most patients when training is properly conducted. It is hardly possible to carry out any effective therapeutic program without encompassing many of the principles involved in a training program of the type described.

#### SUMMARY

The persistent disability in chronic obstructive bronchopulmonary disease is largely mechanical; therefore, drug therapy alone does not provide an adequate approach to treatment. A complete therapeutic program should include extensive patient education in regard to the nature of the disease. Patients should be taught how to achieve effective muscular relaxation and a pattern of slow breathing with emphasis on expiration both at rest and during exertion. The program should provide training in the proper use of nebulized medication, efficient methods of coughing and postural drainage. In properly selected cases, other mechanical aids such as abdominal belts and pneumoperitoneum are valuable. Such a therapeutic plan would thus be based on principles derived from knowledge of the nature of the physiological disturbances induced by the disease.

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## Seminar on Liver Disease

# The Surgery of Portal Cirrhosis of the Liver\*

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THE surgery of portal cirrhosis of the liver consists in treatment of the secondary effects of this disease rather than a direct surgical attack on the primary condition in the liver. This is a discouraging aspect since surgery does not improve the over-all picture of the primary cirrhotic disorder, apart from protecting the liver from repeated insults due to recurring esophageal hemorrhages and the nutritional disturbances associated with ascites. Nevertheless, now that we have had thirteen years of experience with this type of surgery there can be no question that life has been prolonged in many instances, and that the majority of patients have been rehabilitated, with a marked reduction in morbidity.

It is generally agreed that the chief indication for surgical therapy in portal cirrhosis of the liver is prevention of hemorrhage from esophageal varices, a common source of upper gastrointestinal bleeding and frequently the cause of death in the untreated or medically treated patient. The seriousness of esophageal hemorrhage in patients with cirrhosis of the liver has been recognized for many years. Patek, Nachlas and Shull have each reported from three different medical centers that when medical measures alone were used the mortality rate in patients with cirrhosis of the liver after the first hemorrhage from esophageal varices varied from 30 to 50 per cent during the first year. The major causes of death were (1) exsanguinating hemorrhage, and (2) liver failure, in many cases precipitated by esophageal bleeding.

The second indication for surgical therapy in this group of patients is relief of ascites uncontrollable by medical measures. Unfortunately it is only the occasional patient with marked ascites who can be helped by surgical measures. Remarkable improvement can be obtained in many of these patients by utilization of medical

measures including an adequate diet, low sodium intake, use of diuretics and, if necessary, intravenous administration of human serum albumin. Many patients with bleeding esophageal varices, who also have slight to moderate ascites, are relieved of their ascites by the construction of some type of anastomosis between the portal venous system and the systemic venous system. The results in a few other patients with uncontrollable ascites and without esophageal varices have been even more spectacular. This is a select group of patients with ascites which does not respond to medical measures despite a relatively normal level of serum albumin, above 3 gm. per cent.

REVIEW OF SURGICAL PROCEDURES WHICH HAVE
BEEN EMPLOYED IN THE TREATMENT OF
PORTAL CIRRHOSIS

During the latter part of the last century and the first quarter of this century an operation frequently performed, which occasionally seemed to relieve a patient of ascites, was the construction of an omentopexy, or the so-called Talma-Morrison operation. The results of this procedure never were subjected to critical analysis, undoubtedly because of the over-all poor results.

Splenectomy was another method of treating this condition. The rationale for this procedure lay in an attempt to diminish the amount of portal blood entering the splanchnic area and thereby to reduce the portal venous pressure. Unfortunately the effect of this procedure was only temporary and the state of hemodynamics prior to splenectomy redeveloped shortly after the procedure. It should be condemned for another reason, namely, that numerous natural shunts between the spleen and the parietal wall are severed so that actually the patient may be made worse by this procedure. Furthermore, splenectomy may also preclude subsequent

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construction of a portacaval shunt in patients who may require it. Ligation of the splenic artery has slightly more merit than splenectomy, since the numerous natural shunts are not divided, yet the inflow of portal blood is reduced as with a splenectomy. Time has shown, however, that this procedure is useless for a long-term result, and for that reason it has been abandoned.

An attempt to increase the collateral circulation between the esophagus and thoracic structures of the mediastinum and thoracic wall was made by Garlock. His procedure consisted of packing the superior mediastinum with gauze to create an inflammatory reaction, and later removing it. This method also has proved of little or no value.

Attempts have been made to obliterate the esophageal varices by injecting them with sclerosing solutions but this has proved of little value and has been largely abandoned. Esophagogastrectomy and total gastrectomy are procedures recommended by several surgeons for the purpose of removing the source of the blood which enters the esophageal varices. The overall results have not been satisfactory since these procedures carry a high mortality rate in these desperately sick patients and the benefits derived by the very few who survived are very short lived, since bleeding almost invariably recurs.

During the past decade ligation of the hepatic artery has been recommended for the treatment of bleeding esophageal varices and also for relief from ascites associated with cirrhosis of the liver. At the present writing this method of treatment has been abandoned because of its ineffectiveness in preventing esophageal hemorrhage and a high mortality rate resulting from necrosis of the liver. The rationale of the procedure was based on the thought that by reducing the amount arterial blood entering the cirrhotic liver by way of the hepatic artery, the reflux of arterial blood into the portal bed could be reduced. Unfortunately, although this may occur temporarily, nature develops its own collateral circulation and the pre-ligation condition soon returns, so that recurrent bleeding occurs and ascites reforms.

Direct suture of bleeding esophageal varices by transthoracic transesophageal exposure of these blood vessels is a method which has been in use for the past ten years. It is a life-saving procedure in some instances of acute bleeding from varices but unfortunately bleeding recurs in the majority of patients within a relatively short period of time. This procedure has been found to be of greatest value for long-term effects in those patients with bleeding esophageal varices who have normal livers, in the so-called Banti's syndrome group with extrahepatic portal bed block.

One of the more recent surgical procedures to be recommended is total esophagectomy. As yet it has not been performed in a large enough series of patients followed up over a long enough period of time to ascertain its merits. It would appear, however, that this procedure will also prove of little value since it does not primarily alter the pathological physiology of the portal bed hemodynamics by reducing the portal hypertension.

The utilization of cardioesophageal tamponage with an intragastric balloon and/or an intraesophageal balloon is a life-saving method but unfortunately will not prevent recurrence of hemorrhage after the tamponage has been discontinued. It is true that weeks may elapse between hemorrhages but tamponage is in no way a definitive procedure and should be utilized only as an emergency measure in patients with

exsanguinating hemorrhage.

There seems to be little question at this time that the one and only method which offers patients with this disease complex any chance of long-term relief from bleeding esophageal varices is the construction of some type of venovenous anastomosis between the portal venous system and the systemic venous system. Eck, a Russian physiologist, was the first (in 1871) to accomplish such an anastomosis between the portal vein and the inferior vena cava in the experimental animal. It was attempted a number of times afterwards, both in the latter part of the last century and also in the early part of this century, with only one or two instances of survival for a matter of a few months. Longer follow-ups are not recorded in the literature. Undoubtedly the procedure was given up because of inability to construct satisfactory shunts due to the lack of proper instruments and blood vessel sutures. In addition, the serious metabolic and nutritional disturbances associated with cirrhosis of the liver, which complicate this type of surgical procedure, were not understood and as a result the patients died of liver failure. Improvements in anesthesiology have also taken place since then, which enable us today to perform these procedures with much less risk. It has since been proved conclusively that construction of either a direct anastomosis between the portal vein

and the inferior vena cava, or one between the splenic vein and the left renal vein after splenectomy, will prevent bleeding from esophageal varices in the great majority of patients who have a history of esophageal hemorrhage. We now have a sufficient follow-up period in many of our patients to demonstrate that these types of procedures significantly prolong life beyond the first year after operation.

One of the chief criticisms of all the other methods enumerated is that none of them effectively decompress the portal bed by reducing the state of portal hypertension. For this reason it is believed that they should all be abandoned except cardioesophageal tamponage and transthoracoesophageal suture of the esophageal varices, which are useful procedures for emergency control of the severe, exsanguinating type of esophageal bleeding. Their use should be limited to this indication.

#### EMERGENCY TREATMENT

Any discussion of the surgery of cirrhosis of the liver would be incomplete without considering the emergency treatment of a patient with exsanguinating hemorrhage from esophageal varices, because of the high mortality rate in these patients when treated by conservative measures. The following statistics collected at the Massachusetts General Hospital in the fiveyear period from 1946 to 1950 inclusive reveal an appalling mortality rate in cirrhotic patients with acute, severe esophageal bleeding. During this period sixty-five patients were admitted to the hospital because of portal cirrhosis with bleeding esophageal varices. Some type of portacaval shunt was performed in thirty-three (51 per cent). The other thirty-two (49 per cent) died either directly or indirectly from esophageal hemorrhage while attempts were being made to prepare them for shunt surgery. Exsanguination was the cause of death in twenty-three (72 per cent) of these cases, and in the other nine (28 per cent) it was a major contributing factor to their deaths, due to liver failure.

For this reason, since then patients with severe, exsanguinating esophageal hemorrhage have been treated as surgical emergencies. The following procedure in these cases has been carried out. First, cardioesophageal tamponage is instituted by the use of an intragastric balloon. By this means it is usually possible to stop bleeding from esophageal varices in a few minutes by applying a 2-pound weight to the end of the

balloon tube after the balloon has been inserted into the stomach and inflated. It is recommended that when this has been accomplished the patient's blood volume should be restored by repeated blood transfusions, the operating room is prepared, and in a matter of a few hours the patient, unless in impending liver failure, is taken to the operating room and the esophageal varices are sutured through a transthoracic transesophageal exposure. It is recommended that the operative procedure be carried out in this manner as soon as possible, rather than waiting to see if bleeding will recommence when the tube is removed in twenty-four or forty-eight hours, which not infrequently occurs and when it does the patient is usually in a much worse condition to withstand surgery of this magnitude.

It is recommended, therefore, that if cardioesophageal tamponage with a balloon tube is necessary to save a patient from exsanguinating hemorrhage, an emergency operation to suture the esophageal varices should be performed without delay. Fortunately not all patients with bleeding esophageal varices hemorrhage in this manner, so that it is not always necessary to carry out tamponage or emergency surgery. The decision as to which patients should have their esophageal varices sutured should be made by selecting only those in whom it has been necessary to institute balloon tamponage to control the esophageal hemorrhage.

This procedure is not a definitive one and for that reason should be considered only the first stage of a two-stage operative program. Fortunately it controls the bleeding in the majority of patients for a period of six weeks to two months, thereby permitting more thorough preparation of the patient for the larger surgical procedure of constructing some type of portacaval shunt. During the past seven years approximately thirty patients have been treated by this plan. Twenty-four (80 per cent) survived the procedure. This is a great improvement over the pre-ligation statistics which showed that 49 per cent of all patients admitted to our hospital with bleeding esophageal varices died without the benefit of shunt surgery. Unfortunately, all surgeons are not sufficiently trained in the problems of esophageal surgery to perform safely this type of operative procedure, so that if one is not available it is probably better to resort to balloon tamponage alone with the hope that bleeding will not recommence once the tamponage is discontinued.

THE SELECTION OF PATIENTS FOR PORTACAVAL SHUNT

The construction of a splenorenal or a direct shunt to bypass the portal blood around the site of a portal bed block is believed to be the most satisfactory definitive method to stop further hemorrhage from esophageal varices. It should be emphasized therefore that every patient who has bled from esophageal varices should be considered a candidate for some type of portacaval shunt rather than for any other operative procedure or method of therapy. It is of the utmost importance that each patient be carefully evaluated from the standpoint of liver function prior to surgery, since selection of the time for shunt surgery is critical, especially in those patients who are in generally depleted condition with a failing liver and in whom operation must be delayed until they have been

properly prepared.

The following liver function tests, in the order of their importance, are the ones which are used routinely in our clinic to determine the operability of these patients: (1) the serum albumin, (2) the presence of ascites and whether or not it fails to respond to medical therapy, (3) the cephalin flocculation test, (4) the prothrombin time, (5) the serum bilirubin level, and (6) the bromsulphalein® retention test. The serum albumin level is considered the most significant test in determining the operability of the patient, since in six patients with a level below 3 gm. per cent there were five deaths following shunt surgery from operative and postoperative hemorrhage, a mortality rate of 83 per cent, whereas in a group of sixty-nine patients with a level above 3 gm. per cent there were only six operative deaths, or an operative mortality of just 9 per cent. As the result of these experiences it is our rule now that the serum albumin level must be above 3 gm. per cent in all patients who undergo shunt surgery. If it is not, appropriate measures are instituted to elevate it, including the intravenous administration of human serum albumin concentrate. Since the presence of ascites to some degree also is a measure of liver function, suggesting inability of the liver to synthesize the normal levels of serum albumin, it is considered of serious significance, especially if it does not respond to medical measures. When ascites is present every effort is made to clear it by means of medical treatment, including the intravenous administration of the human

serum albumin concentrate. The cephalin flocculation test has proved of great value in predicting the operability of these patients since in thirty-six, with values of 3-plus or 4-plus, there were eleven deaths, or a mortality rate of 21 per cent, whereas in thirty-nine patients with a 1-plus or 2-plus cephalin flocculation test there were no deaths. When the prothrombin time is prolonged, and does not respond to vitamin K therapy, severe liver disease is presumed to be present. The bilirubin level in the blood is of significance when it is considerably elevated; in the majority of patients who are grossly icteric surgery is usually deferred until the jaundice clears. The bromsulphalein retention test is a measure of the excretory function of the liver, and has not been found as valuable in predicting the outcome of shunt surgery, unless there is 20 per cent or more retention, which usually indicates a severely damaged liver. The decision as to whether or not to operate on a patient with a seriously damaged liver does not depend only on the results of one or two of these liver function tests, except when the serum albumin level is below 3 gm. per cent, but also on the over-all condition of the patient as well. It is to be pointed out again that we do not select our patients for shunt surgery, but instead we select the optimum time for it with each patient.

#### RESULTS OF SHUNT-PROCEDURES

Shunt surgery has been performed in 173 patients with bleeding esophageal varices secondary to cirrhosis of the liver, many of whom have been followed up for a sufficient period of time to determine the value of this type of surgical treatment. There were twenty-one deaths, or an operative mortality rate of 12 per cent. These early postoperative deaths were in part due to uncontrollable hemorrhage from the operative field. The majority of them occurred early in the development of this type of surgery. This cause of postoperative death fortunately has been conquered since in the past five years, in ninetythree operative shunt procedures, there have been no deaths from postoperative hemorrhage. The use of one to three fresh blood transfusions during the operation to replace in part the blood loss, and the use of hypotensive spinal anesthesia administered according to the Gillies' technic to reduce the blood loss during the operation, have been important measures in preventing postoperative deaths from this complication. In this group of 173 operative procedure the spleno-

renal type of shunt was performed in 122 patients, whereas in fifty-one a direct anastomosis between the portal vein and the inferior vena cava was accomplished.

The end-to-side splenorenal shunt is preferred in the majority of patients, first because the immediate and late mortality rates following this type of procedure have been less than in those in whom a direct portacaval anastomosis was performed; and secondly, the morbidity of the shunt procedure from neuronutritional disturbances seems to have been less following splenorenal shunt than after the direct portacaval type. The reasons for preferring the latter type are, first, it is easier for the average surgeon to construct this type of anastomosis than the splenorenal type because the vessels are larger and of tougher structure, and, secondly, the incidence of postshunt bleeding has been less for the entire series. With added experience it is believed that the surgeon should choose the procedure which is best for the patient rather than for his own convenience; it should be pointed out that during the past nine years the incidence of postshunt bleeding, even in the splenorenal group, has been less than 5 per cent, a figure comparable to the direct portacaval group.

#### POSTSHUNT ESOPHAGEAL BLEEDING

The true value of portacaval shunt surgery in the prevention of esophageal bleeding can be determined best by an analysis of the results obtained in those patients who have survived and could be followed up for a year or longer after the shunts were performed. It has been possible to determine this in sixty-six patients who have had end-to-side splenorenal anastomoses, and in twenty-six patients after direct portacaval anastomoses. These patients have been followed up from one to nine years after the shunts were constructed. Recurrent esophageal bleeding occurred in eleven (17 per cent) of the patients who had splenorenal shunts. It was mild, not requiring transfusions in four (6 per cent) of them, and major in seven (or 11 per cent). Two of these patients died of massive hemorrhage approximately one year after the splenorenal shunt was constructed. This makes a postoperative mortality rate from esophageal bleeding of 3 per cent, a great improvement over the death rate from esophageal bleeding in the natural course of the disease or in those treated by medical measures alone. Recurrent bleeding was less common following direct portacaval

anastomosis. There were no episodes of minor bleeding in twenty-six patients, and in only three (12 per cent), did major bleeding develop; it is significant that in each of these the portal vein was found to be thrombosed and a thrombectomy was necessary in order to construct the shunts.

In summary, then, it is to be noted that post-shunt bleeding developed in fourteen of a group of ninety-two patients (15 per cent) who had been followed up from one to nine years after the shunts were constructed. The bleeding was major in ten (11 per cent), two (2 per cent) succumbing to esophageal hemorrhage, and it was minor in the remaining four (4 per cent). In contrast to these statistics it is to be pointed out that severe recurrent esophageal bleeding developed in every one of nine patients in whom shunts were attempted but could not be constructed because of diseased portal veins and previous splenectomies.

#### SURVIVAL

It is recognized that it is difficult to compare two groups of cases collected in two different periods, even though they are from the same institution. However, it seems of significance to compare the survival rate in a group of patients collected at the Massachusetts General Hospital from 1934 to 1945 who were admitted because of bleeding esophageal varices secondary to cirrhosis of the liver and who were not subjected to shunt surgery, but treated with conservative measures, with the survival rate in another group of patients treated either by a splenorenal or a direct portacaval shunt. In the first group at the end of the first year there was a survival rate of 50 per cent, which was reduced to 20 per cent at the end of five years. Comparing the shunt group with this, one finds that (including the early postoperative deaths) there was a survival of 80 per cent at the end of the first year and 50 per cent after five years. The difference in these survival rates, it seems, is highly significant and encouraging, but of course further observation over longer periods of time in a larger group of cases is indicated.

#### LIVER FUNCTION

Liver function studies have been carried out in eighty-two patients following shunt surgery. As compared with the preoperative levels the serum albumin level in sixty-two determinations has been found to be higher in 29 per cent, unchanged in 53 per cent, and lower in 18 per cent.

The serum bilirubin levels have been determined in sixty-one patients. Thirty per cent showed improvement, 50 per cent were the same, and 20 per cent had increased levels. The cephalin flocculation test was performed in sixty-one patients, and revealed improvement in 40 per cent, in another 40 per cent it remained the same, and in 20 per cent it was worse than before the operation. The bromsulphalein retention test, 5 mg. per kg. of body weight, was performed in forty-eight patients. Twenty-three per cent of them showed improvement, 31 per cent no change, and 46 per cent showed increased impairment of this test. The hemoglobin determination in seventy-four patients was found to be 12 gm. per 100 ml. or higher in all except ten, and in only three of them was it below 11 gm. per 100 ml.

In a group of seventy-eight patients with cirrhosis of the liver and bleeding esophageal varices in whom splenorenal or direct portacaval shunts were constructed and who have been followed up from one to eight years, fifty-two (67 per cent) were able to return to full time work, seventeen (22 per cent) were able to do part-time work, and seven (9 per cent) were not able to work because of age or disability secondary to their liver disease. As further evidence of the reduction in morbidity of this disease complex the following figures for forty-three patients demonstrate the marked reduction in blood replacement that was necessary following shunt surgery. There were 104 bleeding episodes recorded before the shunts were performed in these forty-three patients, requiring ninety-two hospitalizations; of these bleeding episodes eighty-four were major ones requiring multiple transfusions. According to the records, 523 transfusions had been given to these forty-three patients before shunt surgery was performed. Following the shunt surgery some postshunt bleeding developed in only three patients, or 7 per cent of them. There were only four episodes of bleeding as compared to the 104 such episodes prior to shunt. Only three hospitalizations were necessary, two patients with major bleeding required transfusions. In all, twelve transfusions were given to this group of forty-three patients following their shunt surgery as compared to 523 in the preshunt period.

#### LATE POSTSHUNT DEATHS

Follow-up from one to nine years has been possible in 119 patients who survived shunt

surgery, eighty-five of whom had splenorenal shunts and thirty-four direct portacaval shunts. In this group there have been twenty-six late deaths, or a late mortality rate of 22 per cent. There were fifteen deaths in the group of eightyfive patients with splenorenal shunts, or a total mortality rate in this group of 18 per cent. Five (6 per cent) of the deaths were due to liver failure, two (2 per cent) were secondary to bleeding esophageal varices, eight (9 per cent) were due to other causes unrelated to their liver disease. In the group of patients with direct portacaval shunts, six (18 per cent) died from liver failure, and there were no deaths from esophageal hemorrhage; however, there were two deaths (6 per cent) from cerebral hemorrhage with very low prothrombin levels, evidence of severe liver disease. Three deaths (9 per cent) were from other causes unrelated to the liver disease. Comparing the two groups, therefore, in which it was thought that the deaths were related to their liver disease, in the splenorenal group there were seven deaths (8 per cent), whereas in the direct portacaval group there were eight deaths (24 per cent).

The question is often asked, "Why do you perform more splenorenal shunts than direct portacaval shunts?" These figures on late postshunt deaths constitute one of the reasons, namely, that there seems to be an increased mortality rate in patients with a direct portacaval anastomosis in whom the portal blood bypasses the liver completely, as compared to the splenorenal type in which a partial shunt is constructed. Furthermore, in a group of 152 operative cases in which 108 patients had splenorenal shunts, there were nine early postoperative deaths, a mortality rate of 8 per cent, whereas in forty-five patients with direct portacaval anastomoses there were nine operative deaths, or a postoperative mortality rate of 20 per cent. Thus both the early and late postoperative mortality rates were higher in the direct portacaval group, and it is for that reason, despite the fact that it is more difficult to construct a splenorenal shunt, that the latter is preferred.

#### SUMMARY

Transthoracoesophageal suture of bleeding esophageal varices is recommended as an emergency life-saving procedure in those patients in whom exsanguinating hemorrhage develops from esophageal varices and in whom it is necessary to institute cardioesophageal tam-

ponage with a balloon type of tube. In this way it is possible to control the bleeding vessel and then institute medical measures to prepare the patient for shunt surgery, usually within a period of four to six weeks.

The most effective definitive treatment of bleeding esophageal varices secondary to cirrhosis of the liver that has yet been developed is the construction of either a splenorenal or a direct portacaval anastomosis. The results to date in our clinic with this method of surgical therapy have been extremely encouraging. The life of the cirrhotic patient has been prolonged and the incidence of bleeding greatly reduced. In a few patients with uncontrollable ascites, despite their ability to maintain a normal serum albumin level, the construction of a splenorenal shunt has produced spectacular results in the relief of ascites.

It should be emphasized that the success of this type of surgery in many of these critically ill patients demands the closest cooperation of the internist, the surgeon and the anesthesiologist.

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# Clinico-Pathologic Conference

# Alcoholism, Diarrhea, Osteoarthropathy, Hepatomegaly, Fever and Sudden Death

S TENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

This fifty-seven year old Negro man was admitted to Barnes Hospital for the first time on October 27, 1957; he died seven hours later. He was confused and incoherent, therefore the history of his acute illness had to be obtained from his sister.

For twenty-five to thirty years the patient had had a heavy alcoholic intake consisting of beer, wine, and whiskey. His nutritional intake had been rather poor, but he had never had jaundice, abdominal swelling or edema of the ankles. In 1955 he had ceased drinking. He had been unable to work since 1950 because of malaise, arthralgias, and fatigue. He had remained active, however, until approximately six weeks prior to admission when anorexia, increasing weakness, fatigue and lethargy developed, and he was confined to bed. Subsequently he ingested almost no food, lost a considerable amount of weight, and complained of constipation. Early in October he became apathetic and occasionally confused; it was necessary for his sister to look after him. During the two days prior to admission his speech became slurred and he seemed extremely forgetful. He complained of vague pain in the right upper quadrant of the abdomen.

The following history was obtained from the records of the Homer G. Phillips Hospital in which the patient had been followed up for approximately three years. He had been seen twice in the clinics in 1954, complaining of constipation, terminal dysuria, and non-painful swelling of his penis. During that year he had had two episodes of diarrhea lasting two weeks, associated with intermittent pain in the lower part of the abdomen. No diagnosis was made and treatment was symptomatic. During a clinic visit in February, 1955, he had complained of

vague joint pains, leg cramps, occasional diarrhea, and dizziness. Laboratory studies at that time included a cardiolipin test for syphilis which was negative and a chest roentgenogram which showed a 3 cm. calcified pleural plaque in the lower right side of the chest. In December, 1955, the patient had been seen again complaining of vague pains in his joints and chest, mild exertional dyspnea, and headaches. His blood pressure was 136/90 mm. Hg and the remainder of his examination was within normal limits. An electrocardiogram revealed left ventricular enlargement by voltage alone. During 1956 his predominant symptoms were leg cramps and arthralgias. A joint examination was completely normal. In January, 1957, he attended the clinic because of frequency, urgency, nocturia seven times per night, and persistence of dizzy spells and leg cramps. Examination revealed no abnormalities other than an enlarged prostate. Cystoscopy showed hypertrophy of the neck and trigone of the bladder. A transurethral resection was advised but was refused.

The patient had been admitted to the Homer G. Phillips Hospital for the first time from February 24, 1957 to February 25, 1957 for suture of a 3 cm. laceration on the dorsum of the right wrist, which had been incurred during a fight while he was intoxicated. Examination showed no abnormalities except for an 8 cm. scar on the right flank (history concerning this unknown). The liver, kidney and spleen were not palpable. He had a hemoglobin level of 8.3 gm./100 ml., and a white blood cell count of 5,300/cu. mm. The patient was given 150,000 units of antitetanus serum and antibiotics.

His second hospitalization at Homer G. Phillips Hospital had been from June 9, 1957 to

June 26, 1957. For the two months prior to this admission, he had suffered from severe aching pains in both hip joints, legs, arms, and shoulders without objective changes. He also had anorexia and had lost an unknown amount of weight. No other symptoms relating to this illness are known. Physical examination revealed a blood pressure of 110/55 mm. Hg; pulse, 34/minute; respirations, 20/minute; and temperature, 101.8°F. No abnormalities were detected when his heart and lungs were examined. The liver was palpable two fingerbreadths below the right costal margin and was slightly tender. Flank tenderness was present bilaterally. The spleen was not palpable. Clubbing of the fingers was described by one observer. Laboratory studies revealed a hemoglobin of 8.2 gm./100 ml.; mean corpuscular volume, 96 cu. microns; mean corpuscular hemoglobin, 27 gamma gamma, and mean corpuscular hemoglobin concentration, 28 per cent. The white blood cell count was 8,900/cu. mm. Urinalysis revealed a specific gravity of 1.005; traces of albumin, sugar, and acetone; 10 to 15 epithelial cells; and occasional white blood cells in the sediment. Bleeding time was three minutes and clotting time was eight minutes. The prothrombin level was 98 per cent of normal. The blood urea nitrogen was 10 mg./ 100 ml.; total serum proteins, 5.5 gm./100 ml.; with an albumin-globulin ratio of 2.6/2.9; total bilirubin, less than 0.8 mg./100 ml., alkaline phosphatase, 3.7 Bodansky units; thymol turbidity test, 5.1 units; phosphorus, 2.7 mg./100 ml.; and the serum icterus index was normal. Alpha streptococci were cultured from the sputum. The cardiolipin test was negative and stools were guaiac negative. The chest roentgenogram revealed parenchymal scarring of the right perihilar region with calcification and a right pleural plaque. A search for metastases was negative. Agglutination studies for typhoid H and O antigens were positive in dilution of 1:80, and proteus OX-19 was positive in dilution of 1:30. Proctoscopy was normal to 20 cm. The patient was treated with aqueous penicillin, 100,000 units administered four times daily for four days and became afebrile.

The third admission to Homer G. Phillips Hospital was from September 1, 1957 to October 12, 1957. For the previous four months, he had complained of slight tenderness and dull intermittent aching pain in the right upper quadrant of the abdomen, not associated with food ingestion, nausea, or vomiting. There had been no

change in bowel habits and no melena. During this period he had lost 20 pounds in weight. Twelve hours prior to this admission abdominal cramps developed suddenly with sharp non-radiating pain in the right upper quadrant, and fever but no chills. He had had minimal edema of the ankles for several days.

The vital signs included a blood pressure of 188/70 mm. Hg. and a temperature of 101.4°F. There was moderate scleral icterus. Dullness, decreased breath sounds, and moist rales were detected. The heart was thought to be normal. The liver was palpable four fingerbreadths below the right costal margin and was tender, particularly in the epigastrium. No edema of the ankles was described. The hemoglobin was 8.9 gm./100 ml. but subsequently increased to 9.8 gm./100 ml. The white blood cell count was 10,400/cu. mm. with a differential pattern of 10 per cent band forms, 63 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes, and 2 per cent monocytes. A subsequent white blood cell count was 14,250/cu. mm. The blood urea nitrogen was 10 mg./100 ml. and the thymol turbidity test was 6.0, 3.1 and 4.8 units on three separate examinations. Total serum proteins were 6.0 gm./100 ml. with a globulin level of 4.0. The serum bilirubin was 0.2 mg./ 100 ml. direct and 1.4 mg./100 ml. indirect; bromsulphalein® retention was 24 per cent in forty-five minutes. Urinalysis revealed bilirubin and urobilinogen to be present; tests for proteins and glucose were negative. A roentgenogram of the abdomen demonstrated hepatomegaly. Oral cholecystograms and intravenous cholangiograms showed no dye in the gallbladder or biliary tree although there was prompt appearance of the dye in the kidneys.

During the hospital course, pain and tenderness persisted in the right upper quadrant of the abdomen although it decreased in intensity. The temperature varied from 97.0° to 102.0° F. (oral temperatures). Treatment consisted of penicillin, 600,000 units administered twice a day from September 9, 1957 to October 12, 1957; tetracycline, 250 mg. administered twice a day, from October 1, 1957 to October 12, 1957; streptomycin, 1.0 gm. per day, from September 1, 1957 to October 12, 1957, and vitamin B<sub>12</sub>, 100 µg. daily during the entire stay. The patient did not appear to improve on this therapy; he was still icteric and had a temperature of 100° F. when he was sent home.

The patient was admitted to Barnes Hospital on October 25, 1957 just two weeks following his discharge from the Homer G. Phillips Hospital. The physical examination revealed a temperature of 35°c.; respirations, 16/minute; pulse, 120/minute (regular); blood pressure 100/70 mm. Hg. He appeared chronically ill, wasted, confused and disoriented. There was prominent scleral icterus. The skin was cool and fine but not clammy. There were two small lesions over the upper posterior thorax suggestive of spider angiomas. There were no liver palms and the hair distribution was normal. Small, shotty lymph nodes were present in both axillae. The pupils were miotic, irregular, and unresponsive to light. Funduscopic examination showed moderate arteriosclerotic changes. The ears, nose and mouth were normal except for carious teeth and moderate dehydration of the mucous membranes. The neck was supple and there was minimal venous distention at a 30 degree angle from the horizontal. Both carotid pulses were palpable. The thyroid gland was not palpable and the trachea was in the midline. There was flatness to percussion over the lower third of the right lung field with decreased vocal fremitus, absent breath sounds, and an occasional crackle over this area. No change in level of flatness occurred with inspiration. The remainder of the lung fields were hyperresonant to percussion. The heart did not appear enlarged; sounds were distant, and there was a high pitched crackling, leathery sound heard at the apex when the patient was in the supine position. This sound was heard along the right and left sternal borders and in the aortic area; it extended throughout systole but was not heard in diastole. There was no gallop rhythm or pulsus paradoxicus. The abdomen was distended and tympanitic. The liver was palpated 7 cm. below the right costal margin in the midclavicular line and 9 cm. below the xiphoid process. The splenic tip was palpated at the left costal margin. The kidneys could not be felt. There was no fluid in the abdomen. No bowel sounds were audible. The prostate was two times enlarged, firm and slightly nodular. The rectal ampula was filled with light colored feces; no rectal shelf was palpable. The genitalia were normal. Examination of the extremities showed early clubbing of both fingers and toes, 1 plus edema of the left ankle, trace edema of the right ankle, and presence of all peripheral pulses. There was no flapping tremor. The deep tendon reflexes were

hyperactive and bilaterally equal; no pathological reflexes were obtained.

Laboratory data were as follows: hemoglobin, 7.1 gm./100 ml.; hematocrit, 19 per cent; red blood cell count, 2.5 million/cu. mm.; white blood cell count, 39,000/cu. mm. with a differential pattern of 1 per cent myelocytes, 6 per cent metamyelocytes, 36 per cent band forms, 49 per cent polymorphonuclear leukocytes, 1 per cent eosinophils, 1 per cent basophils, 3 per cent lymphocytes, and 3 per cent monocytes. The stained peripheral blood film showed moderate anisocytosis and poikilocytosis, many target cells, and an adequate number of platelets. The blood cardiolipin reaction was negative. The stool was trace positive to guaiac. A urinalysis was not done. Red blood cell constants showed mean corpuscular volume, 76 cu. microns; mean corpuscular hemoglobin, 28 gamma gamma; and mean corpuscular hemoglobin concentration, 37 per cent. The nonprotein nitrogen was 64 mg./100 ml. (blood urea nitrogen, 44 mg./100 ml.); blood sugar, 106 mg./100 ml.; serum sodium, 138 mEq./L.; potassium, 3.9 mEq./L.; chloride, 103 mEq./L.; carbon dioxide, 19.5 mEq./L.; and cholesterol, 70 mg./100 ml. Liver function tests showed the following: cephalin cholesterol flocculation, 3 plus; thymol turbidity, 9.9 units; alkaline phosphatase, 10.4 Bodansky units; serum albumin, 2.5 gm./100 ml.; globulin, 4.8 gm./100 ml.; direct bilirubin, 0.8 mg./100 ml.; indirect bilirubin, 0.7 mg./100 ml.; and amylase, less than 50 units. The serum calcium was 8.3 mg./ 100 ml. and the phosphorus was 6.8 mg./100 ml. The patient's blood type was O Rh positive. An electrocardiogram showed an abnormal form of ventricular complex. Roentgenographic studies revealed that the heart was slightly enlarged and a 1.3 by 3 cm. density was seen in the right lateral chest thought to be calcified pleura; the stomach was distended with gas and contained an air fluid level; there were a few air fluid levels in small bowel loops; the cecum was filled with gas and appeared to be deformed; the liver was greatly enlarged with the lower edge extending below the pelvic brim.

Shortly after the patient's admission to the hospital, a Levin tube was inserted into his stomach and approximately 600 cc. of air and 500 cc. of greenish guaiac negative material were removed. Free acid was present in this material. Five hours after admission, the patient was noted to be more disoriented and confused,

and was complaining of severe pain in the right upper quadrant of the abdomen. He was given 50 mg. demerol<sup>®</sup> intramuscularly. Twenty minutes later his respirations ceased and he died.

#### CLINICAL DISCUSSION

DR. EDWARD REINHARD: This fifty-seven year old man presented with a long history of alcoholism and presumably poor dietary habits. He complained of arthralgias and fatigue for about five years. There was a history of leg cramps, occasional bouts of diarrhea, attacks of dizziness, chest pain, and dyspnea on exertion for perhaps two years. He had symptoms of prostatism for ten months, for which surgery had been advised and refused. He had an anemia of about 8 gm. of hemoglobin for at least eight months. He had intermittent attacks of pain in the right upper quadrant of the abdomen as well as some generalized abdominal pain for a period of about five months. He had anorexia, weakness, fatigue, lethargy, and weight loss for four months, most marked during the six weeks preceding admission. During the last two weeks, he showed mental confusion. For two days, he had slurred speech, very profound forgetfulness and was at times quite incoherent. He died seven hours after admission to Barnes Hospital. Dr. Humphrey, will you review the roentgenograms obtained at Homer Phillips as well as at Barnes Hospital?

DR. HARVEY A. HUMPHREY: An abdominal roentgenogram taken in September, 1957, showed a markedly enlarged liver. The lower pole of the liver extended into the iliac fossa. There was some deformity of the gas shadows in the upper part of the abdomen, presumably due to hepatic enlargement. This degree of enlargement seemed a little unusual for uncomplicated advanced cirrhosis and suggested an associated tumor mass. An oral cholecystogram failed to visualize the gallbladder. Calcification in the right pleural space was noted and presumed to be either postinfectious or post-traumatic in origin. In October, 1957, intravenous pyelograms showed prompt and very good excretion of dye by both kidneys. The basal urinary bladder appeared elevated suggestive of an enlarged prostate. The renal calyces appeared a little deformed, probably due to extrinsic pressure by the enlarged liver. The roentgenograms taken at Barnes Hospital showed a grossly enlarged stomach filled with gas and fluid. This gastric dilatation may have represented a gastric or adynamic ileus due either to duodenal or to

pyloric obstruction. We have no studies to either confirm or deny that possibility. A portable roentgenogram of the chest showed a normal sized heart. The plaque of calcification was noted on the anterior aspect of the right lung. Moderately pronounced arteriosclerosis and some degenerative arthritis was also noted.

DR. REINHARD: Dr. Goldman, I think the localized area of calcification in the pleura is rather remarkable. Would you comment on its nature and possible cause?

DR. ALFRED GOLDMAN: In general, the two most common causes of such calcifications are trauma with hemorrhage into the pleural cavity, and tuberculous pleurisy with or without actual empyema. Apparently pyogenic infections may also produce such a picture. There is one less well known cause and that is inhalation of certain dusts, particularly, talc and mica. In talc workers, something like 6 per cent of the men will show such calcification. In some cases it is bilateral. Without a more complete history, it would be impossible to comment further on the etiology of this calcification.

DR. REINHARD: You will recall that this patient had early clubbing of both fingers and toes. Clubbing is a mysterious phenomenon. Dr. Smith, would you comment on what is known about its pathogenesis and the types of disorders with which it may be associated?

DR. JOHN SMITH: The phenomenon of clubbing is part of a much larger syndrome of osteoarthropathy which includes periosteal changes in the phalanges of the hands and feet, joint pains, hydrathrosis and sometimes a remarkable display of autonomic instability with sweating and flushing. The clubbing itself is a mysterious process when it occurs. It sometimes is seen in persons without obvious disease. It is usually found in association with chronic pulmonary or cardiac disease particularly when there is unremitting cyanosis. It is also seen in infections, such as subacute bacterial endocarditis. It has been described in certain types of liver disease, particularly biliary cirrhosis, although some people think they have seen it in Laennec's cirrhosis also. Its occurrence in liver abscesses and in disease with widespread hepatic parenchymal destruction is not unusual. Clubbing also occurs in starvation states, particularly those associated with chronic diarrheas and probably chronic avitaminoses. Its cause is unknown. Anoxemia has been postulated as a mechanism but this explanation has never been

satisfactorily borne out. Some have postulated that an abnormal secretion of the pituitary growth hormone is responsible but supporting evidence is lacking. I have often wondered whether or not there is an association with adrenal cortical hormonal secretions, particularly in the course of infections.

Dr. Reinhard: Let us now focus attention on the hematologic findings. In February, 1957, the hemoglobin was 8.3 gm. per cent and the white blood cell count was 5,300/cu. mm. We have no other data. In June, 1957, no change in values was noted. In September, 1957, the hemoglobin remained unchanged and the white blood cell count was 10,400. The differential at this time was normal. At the Barnes Hospital during the patient's final seven hour admission, the following data were obtained: hemoglobin was 7.1 gm. per cent; hematocrit was 19 per cent, the red blood cell count was 2.5 million per cu. mm. A marked leukocytosis with a shift to younger forms in the granulocytic series was noted for the first time. Platelets were not counted but were said to be normal on the blood film. Moderate anisocytosis, poikilocytosis and many target cells were described. Dr. Moore, would you discuss the possible factors that might have contributed to the anemia in this patient?

DR. CARL V. MOORE: We are handicapped by not having either a reticulocyte count or a bone marrow examination. Since there was no hypochromia, the anemia was probably not due to chronic blood loss from the gastrointestinal tract, and can probably be related to hepatic disease. Recent work indicates that anemia under these circumstances is a combination of at least two factors: a hemolytic component and relative marrow hypoplasia. The marrow may actually be forming a normal number of red blood cells but has not increased its rate of erythropoiesis to compensate for the hemolysis. Therefore, on the basis of the information we have, I would guess that this was an anemia, explainable either on the basis of hepatic disease or of a neoplasm. The comments made about the mechanism of anemia in hepatic disease would apply equally well to that of a secondary neoplasm.

DR. REINHARD: What about chronic infection as a cause?

DR. MOORE: On the basis of the information we have in the protocol, that would be somewhat less likely than the other two possibilities mentioned.

Dr. Reinhard: We can exclude azotemia as

the cause of the anemia since the anemia definitely preceded the azotemia. Dr. Moore, would you discuss the marked leukocytosis with a shift to the younger forms?

DR. MOORE: These changes were a terminal manifestation of something which happened during the last weeks of life. We are justified in calling them a leukemoid reaction, in spite of the fact that nucleated red cells were not observed in the peripheral blood. The most likely cause of such a reaction in this patient would seem to be a neoplasm, with or without metastases to the bone marrow. Severe peritoneal inflammation might also cause such a reaction and the patient had evidence of intestinal obstruction with considerable tenderness in the abdomen.

DR. REINHARD: The primary problem is the nature of the hepatic lesion. We may assume that this patient had severe liver disease. The history of alcoholism and an inadequate diet would point strongly towards Laennec's cirrhosis but there are other possibilities that should be considered. No liver function studies were available prior to June, 1957, at which time the serum albumin was low, while serum globulin, thymol turbidity test, alkaline phosphatase and prothrombin levels were all normal. On admission to Barnes Hospital, the cholesterol level was low, cephalin cholesterol flocculation test was 3 plus, thymol turbidity test was 9.9 units, alkaline phosphatase was elevated to 10.5 Bodansky units and the patient had, in addition to hypoalbuminemia, marked elevation of serum globulin. The bilirubin was also elevated and was equally distributed between the direct and indirect reacting fractions. The serum amylase was very low. Dr. Wenneker, do you see any reason to doubt the diagnosis of portal cirrhosis of a nutritional or alcoholic variety?

DR. ALVIN WENNEKER: No, I do not.

DR. REINHARD: How about postnecrotic cirrhosis? Ratnoff and Patek [1] comment on the frequency of a history of alcoholism in such patients. These authors reported a series of patients with postnecrotic cirrhosis and noted that 29 per cent of them were addicted to alcohol. Do you think we may dismiss this diagnosis?

DR. WENNEKER: We cannot exclude the possibility. However, the fact that the patient's serum globulin was not strikingly elevated except terminally is somewhat against the diagnosis.

Dr. Reinhard: The age and sex of the patient

<sup>1</sup> RATNOFF, O. D. and PATEK, A. J., Jr. Postnecrotic cirrhosis of the liver. A study of 45 cases. *J. Chron. Dis.*, 1: 266, 1955.

are also a little in favor of Laennec's cirrhosis rather than the postnecrotic variety.

We have already noted that he had arthralgia and clubbing. If we put these together we may perhaps assume that he had osteoarthropathy. Popper [2] lists the sixteen most common symptoms which are seen in association with cirrhosis. Arthralgia is not included in this listing which was derived from the publications of ten different authors. Dr. Karl, would you comment on the arthralgias and tell us if you think them a manifestation of osteoarthropathy? Further how often does arthralgia occur in cirrhosis?

DR. MICHAEL KARL: On physical examination no evidence of arthritis was present. I wonder if some of the so-called arthralgia might not have been the neuropathy that is so common in cirrhotic subjects, particularly in patients with a poor nutritional history. There are many references throughout the literature to various types of neuropathic syndromes associated with alcoholic cirrhosis. I am not impressed that true arthritis is a manifestation of cirrhosis. There are some references to the association of arthralgia with liver disease and it is interesting that Dr. Paul Klemperer [3], in one of his original descriptions of "catarrhal jaundice" commented that the association with arthritis was extremely high.

DR. REINHARD: With alcoholic neuropathy, one would not expect the pain to be localized in the vicinity of the joints; but if the history was not carefully obtained, the pain might be described as arthralgia. That is a good suggestion. Dr. Karl, why do patients with the pain of arthritis improve when jaundice develops?

DR. KARL: This is rather complicated and was first commented upon by Dr. Hench. The steroid content of bile is presumably responsible and yet Dr. Hench was unable to demonstrate any therapeutic benefits from the administration of bile salts to patients with arthritis.

DR. REINHARD: Popper in his book, summarizes the causes of death in 535 cases of cirrhosis. Infections occur fairly frequently in association with cirrhosis as the cause of death. Peritonitis was present in 4 per cent of patients. Pneumonia was also common. Tuberculosis, tuberculous peritonitis, and erysipelas are not uncommon. Other associated disorders have

been noted. Portal vein thrombosis may occur. Cholelithiasis, peptic ulcer and chronic gastritis are said to occur with increased frequency in cirrhosis.

DR. KARL: The lowered resistance to infection is actually a confusing situation because it has been pointed out many times that patients with cirrhosis are able to make antibody in normal and even in supernormal quantities in response to various antigens. It has been suggested that even though gamma globulin levels are increased, perhaps these are abnormal globulins.

DR. REINHARD: The statement has been made in the literature that the lack of resistance to infection may be related in some way to protein deficiency. I know of no specific data concerning the mechanism.

DR. BERNARD BERCU: There are several points which I interpreted differently. This patient actually had chronic recurrent diarrhea with arthritis for many years and then jaundice and liver disease developed. Under these circumstances there are two diseases which should be seriously considered. One is amebiasis. I recall a case report in which arthritis presented as an initial manifestation of amebiasis. The other possibility would be Whipple's disease in which arthritis, diarrhea and occasionally jaundice occur. I would favor amebiasis because of the absence of a sprue-like syndrome. In addition, it is well known that chronic diseases of the colon are associated with clubbing.

DR. REINHARD: Do you have any further comments on the possibility of amebiasis, Dr. Shatz?

DR. Burton Shatz: Amebiasis is a very good possibility, especially with liver abscess. The points in favor of liver abscess due to amebiasis are recurrent episodes of diarrhea for three years, arthralgia, fever, pain in the right upper quadrant of the abdomen and a rapidly enlarging, tender liver. The low serum amylase and the elevated alkaline phosphatase are characteristic findings in liver abscess. The fact that the patient had an 8 cm. scar on the right flank and calcification in the right pleura, which might be secondary to trauma, brings up the possibility of a stab wound that traversed the right pleural space and entered the liver. This might have served as a route of infection for a pyogenic abscess. However, amebic abscess seems the better choice.

DR. REINHARD: I was also intrigued by the possibility of Whipple's disease. That disease would certaintly account for the diarrhea and

<sup>&</sup>lt;sup>2</sup> POPPER, H. and SCHAFFNER, F. Liver: Structure and Function. P. 522. New York, 1957. McGraw-Hill.

<sup>&</sup>lt;sup>8</sup> KLEMPERER, P., KILLIAN, J. A. and HEYD, C. G. The pathology of "icterus catarrhalis." *Arch. Path.*, 2: 631, 1926.

the joint manifestations. However, I am not aware that Whipple's disease would be apt to produce the severe liver disease which I think this patient probably had.

Dr. Shatz: It would be hard to explain the

extremely large liver.

DR. REINHARD: You recall that approximately 4 per cent of all the patients reported with cirrhosis died with peritonitis. Dr. Karl can you give us any information as to the specific patho-

genesis of peritonitis in cirrhosis?

DR. KARL: I am not sure that the pathogenesis has been clearly worked out, but certainly it is a common observation at autopsy that patients with cirrhosis have edema and lymphangitis of the small bowel. In patients with cirrhosis in whom portal hypertension develops and who are unable to detoxify substances brought through the portal system, inflammation of the small bowel will in turn develop with transudation and migration of bacteria and white cells through the lymphatics. It has been suggested that this is the mechanism of the primary pyogenic peritonitis that is seen.

DR. Sol Sherry: When peritonitis occurs, is it most often seen in patients who have ascites? In the nephrotic syndrome, at least in the old days, peritonitis was a common complication and I wondered whether or not ascites was the common denominator in both situations?

DR. KARL: Yes, that is true. When primary peritonitis is present, it is almost always in association with ascites.

DR. REINHARD: Dr. Karl, we have already mentioned the possibility of liver abscess, either of amebic or pyogenic etiology. Do you think

this is a likely possibility?

DR. KARL: It should certainly be given serious consideration. The patient complained of marked pain in the right upper quadrant. He had fever, leukocytosis terminally and rather marked tenderness in the hepatic area. There are not too many conditions in which there is such marked tenderness in the right upper quadrant, but liver abscess is one of these. Dr. Shatz referred to the fact that the amylase was low. Some years ago a publication from the Jewish Hospital in St. Louis [4] described a small series of patients with liver abscess in whom amylase levels were low even to the point of zero. The same observa-

<sup>4</sup> Gray, S. H., Probstein, J. G. and Heifetz, C. J. Clinical studies on blood diastase. I. Low blood diastase as an index of impaired hepatic function. *Arch. Int. Med.*, 67: 805, 1941.

tion has been made in patients with primary carcinoma of the liver. Liver abscess should be given very serious consideration here.

DR. REINHARD: One would suppose that if patients with cirrhosis are very susceptible to infections, liver abscess would be one of the more common findings in cirrhosis. Is that true?

DR. KARL: No. It is rare.

DR. REINHARD: Let us consider cholelithiasis and cholecystitis next. Dr. Shatz, would you discuss why it is that patients with cirrhosis have an increased incidence of gallstones?

DR. SHATZ: The reason is not clear. Some people believe that with liver disease there is a disturbance in the cholesterol-bile salt ratio. Since bile salts are necessary to keep cholesterol in solution, this disturbance may lead to precipitation of cholesterol. Gallstones, in general, are less common in the Negro race than in the white race. In a recently reported autopsy series of 34,000 cases [5], the incidence in white males was 10 per cent, in white females about 21 per cent. In the Negro, the incidence in males was 3 per cent and in females, 9 per cent. In cirrhosis of the liver, all these percentages go up but since we are concerned today with a Negro male, it should be noted that the percentage only increases from 3 per cent to about 4 per cent which is really insignificant. Gallstones in the Negro male are unusual as we have observed at the Homer Phillips Hospital. In this case, the presence of cirrhosis is not a significant point in directing one towards the diagnosis of gallstones as the basis of this man's trouble.

DR. REINHARD: Dr. Moyer, did you have any comments on the possibility of cholecystitis or cholelithiasis?

DR. CARL MOYER: It has already been said that in this Negro man the likelihood of gall-stones would be exceedingly remote.

DR. Reinhard: Does the roentgenographic diagnosis of reflex ileus help us diagnostically, or is that a common manifestation of any type of abdominal infection?

DR. MOYER: It would not help me because this roentgenogram was obtained very shortly before the patient died and in dying patients such things as acute gastric dilatation are especially apt to develop.

DR. REINHARD: Do you want to comment on what you think this patient did have as the terminal event?

<sup>5</sup> Lieber, M. M. Incidence of gallstones and their correlation with other diseases. *Ann. of Surg.*, 135: 394, 1952.

DR. MOYER: The most likely diagnosis is diffuse carcinomatous involvement of the liver, likely primary carcinoma of the liver. On the film shown by Dr. Humphrey it was seen that the configuration of this liver was normal although it was very large. In my experience amebic abscess or another type of abscess sufficiently extensive to produce enlargement of the liver would change its configuration. Consequently, I suspect this patient died of carcinomatous infiltration of the liver. You might examine the thought as to whether or not he died of portal vein thrombosis. At no time did anyone find any sign of ascites. His terminal course was not compatible with that either. My diagnosis is primary neoplasm of the liver.

DR. REINHARD: Alcohol, in addition to playing a role in the pathogenesis of cirrhosis, is also a factor in the pathogenesis of approximately one half of the cases of acute and chronic pancreatitis. The low serum amylase level does not suggest pancreatitis but I wonder, Dr. Karl, if that diagnosis is not worth considering?

DR. KARL: Yes. I would not be surprised if this patient showed histologic evidence of pancreatitis because it is a common finding in patients dying with cirrhosis. However, I hardly think pancreatitis was a primary factor here.

MISS VIRGINIA MINNICH: Could this patient have had sickle cell-hemoglobin C disease?

DR. REINHARD: That is a very interesting suggestion that had not crossed my mind.

DR. MOORE: Miss Minnich is quite right in pointing out that possibility. Dr. Harrington also mentioned this to me before the conference. One could easily have missed sickling because only an ordinary blood film was obtained. However, if the patient had sickle cell-hemoglobin C disease it was an associated phenomenon with whatever else he had.

DR. REINHARD: Carcinoma of the liver is certainly a diagnosis that must be considered in this case. In about 5 per cent of patients with Laennec's cirrhosis carcinoma of the liver develops. Also 34 to 82 per cent of patients with primary carcinoma of the liver have pre-existing cirrhosis. Dr. Morrison, would you comment on this patient's symptomatology in relation to such a diagnosis?

DR. GEORGE MORRISON: The patient's symptoms could easily fit this diagnosis. One of the outstanding features of primary carcinoma of the liver is the extreme variability in the signs and symptoms. The clinical picture has been divided

into six categories, one of which includes those patients who have no symptoms at all. Of the four cardinal symptoms, the most common is a rapidly growing tender liver without evidence of carcinoma elsewhere in the body. Multiple nodules are more common than a single nodule in the liver although these may not be felt. Characteristically, the diaphragm is elevated. The second most common symptom is abdominal pain. While Sheila Sherlock believes that the pain is dull and rarely severe, among the South African Bantu, in whom the disease is common, the symptoms of pain and tenderness are frequently severe. This pain is thought to be related to hemorrhage or infection about the tumor. The next most common symptom is abdominal distention and, after that, low grade fever, weight loss and evidence of chronic wasting disease. This patient had jaundice to a mild degree; approximately half of the patients with primary carcinoma of the liver have jaundice but usually it is mild. In those patients with ascites, splenomegaly and other evidence of portal hypertension, there is a more marked degree of cirrhosis than this patient evidently had. At death, more than half of the patients have metastases beyond the liver and while metastasis is usually to the regional lymph nodes or the lung, it may also be to the bone which may help to explain this patient's blood picture.

DR. REINHARD: Dr. Wenneker, was hepatic coma the cause of the terminal manifestations or are there some other central nervous system lesions that we should consider?

DR. WENNEKER: We can explain the entire mental and neurological picture on the basis of hepatic cellular failure. He had extensive liver disease as indicated by his clinical course and by the liver function tests. The picture he presented fits fairly well into that described by McDermott as an acute spontaneous encephalopathic type of hepatic coma. However, this patient did have a history of alcoholism and it is very difficult to estimate the amount of alcohol intake just prior to his last admission. We would also have to consider in the differential diagnosis an alcoholic psychosis or Wernickes encephalopathy. The absence of delerium tremens and ophthalmoplegia is against the latter diagnosis.

DR. REINHARD: Dr. Bricker, what are the various factors which may contribute to the development of azotemia in patients who have severe liver disease? Is the azotemia entirely renal in origin?

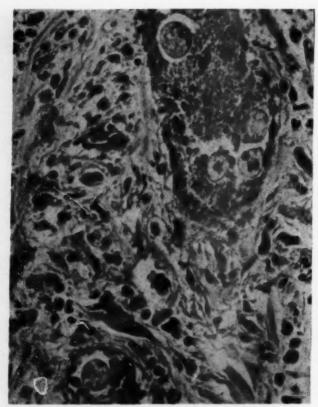


Fig. 1. Portion of the wall of the hepatic abscess. Four trophozoites of E. histolytica are present in an area of necrosis in the upper half of the photograph; a single trophozoite is present in what appears to be a cholangiole near the bottom. There are many inflammatory cells in the highly vascular fibrous tissue. Masson trichrome stain, original magnification  $\times$  360.

DR. NEAL BRICKER: In such a patient as the one today, there may be prerenal factors of import. However, we do not have a good history in this man. He may very well have been dehydrated, had contraction of his plasma volume and from this sustained decrease in glomerular filtration. In the natural history of hepatic disease as hepatic failure develops, we see the picture of acute renal failure which is very similar clinically to acute tubular necrosis although not necessarily similar histologically. These patients almost invariably die.

DR. REINHARD: Our time is up so I will merely comment that there was a pericarditis, most likely uremic in origin. I believe this patient had portal cirrhosis of the liver with an osteoarthropathy. The terminal illness could have been infection of the liver with abscess formation (amebic or pyogenic) and peritonitis. I would be willing to eliminate cholelithiasis and empyema of the gallbladder as diagnostic possibilities. Carcinoma of the liver could certainly

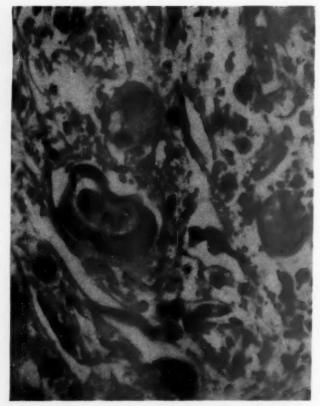


Fig. 2. Two trophozoites of E. histolytica lie in the fibrous wall of the hepatic abscess. Masson trichrome stain, original magnification × 640.

have accounted for all of the findings. I believe we shall find lesions in the kidneys and in the pancreas that are compatible with cirrhosis. Dr. Ahlvin will begin the discussion of the postmortem material.

#### PATHOLOGIC DISCUSSION

Dr. Robert C. Ahlvin: An abscess cavity 8 cm. in diameter was present in the superior portion of the left lobe of the liver. The diaphragm was adherent to the liver adjacent to the abscess. When external pressure was applied to the abscess, its contents were extruded into the inferior vena cava and right atrium through the hepatic vein. The abscess contained brown necrotic semifluid material. The abscess wall was composed of firm fibrous tissue. It was several millimeters thick and thin finger-like projections extended out into the adjacent hepatic parenchyma. The left hepatic vein was continuous with the abscess cavity. Many trophozoites of Endomeba histolytic were present in the abscess wall. (Figs. 1 and 2.) None were found in the necrotic debris of the abscess cavity. Throughout the left lobe of the liver there were areas of recent

central necrosis of liver lobules. No trophozoites were found in these areas. The remainder of the liver was normal.

The main pulmonary arteries were occluded by thromboemboli which were composed of necrotic debris similar to that seen in the abscess. No trophozoites were found in the thromboemboli. These emboli were not organized, however, several thrombi were found in smaller bronchioles of the pulmonary arteries which were undergoing organization. No pulmonary infarcts were present.

There were fibrocalcific nodules and fibrous apical scars of healed tuberculosis. The calcified pleural lesion seen on the x-ray films was directly under the scar on the thorax so that we presume it represents an old hemothorax. No anatomical proof is possible for the assumption.

A slight fibrinous pericarditis was seen over the posterior aspect of the heart. No microorganisms were seen in this lesion and it is believed to be secondary to the inflammatory process in the adjacent organs. The colon was very carefully

examined. No mucosal lesions were present. There was an increased amount of connective tissue with a few chronic inflammatory cells in the submucosa of the cecum and ascending colon. This is interesting in view of the known prediliction of this parasite for the right side of the colon in those few cases in which the entire colon is not involved in the process.

Anatomical Diagnosis. Primary: Submucosal scars in the cecum and ascending colon; amebic abscess of the liver with extensive scar formation and with extension into the right hepatic vein; multiple thromboemboli of abscess contents in all lobes of the lungs; organizing fibrinous pericarditis. Accessory: Focal calcification and ossification of the pleura on the right; diffuse pulmonary emphysema; multiple fibrocalcific nodules in the lung and in tracheobronchial lymph nodes; fibrous apical scars; arteriolar nephrosclerosis, moderate; hypertrophy and dilatation of the heart (420 gm.); arteriosclerosis of the aorta, advanced; of the coronary and renal arteries, moderate.

# The Absorption of Fats, Studied in a Patient with Chyluria\*

I. Clinical Investigation

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Lund, Sweden Copenhagen, Denmark New York, New York

THE first definitive studies of fat absorption were made in man. The classical experiments of Munk and Rosenstein in 1892 [1] were carried out in a patient with a thoracic duct fistula. Since fat absorbed from the intestinal tract was immediately shunted outside the body, it was possible to carry out a unique series of quantitative and qualitative studies of fat digestion and absorption. Subsequently, a number of cases of chylothorax have been observed, but in this condition a precise definition of biochemical events is obscured by the periods of delay between thoracenteses. However, in a recent study of a patient with chylothorax Fernandes et al. [2], by virtue of good experimental design and use of modern analytical methods, were able to reach certain significant conclusions. Their data proved that the fatty acid pattern of the chyle is determined by the composition of the mixture of fatty acids in the dietary fat. Moreover, they found that caprylic acid (C<sub>8</sub>) was not absorbed via the thoracic duct but presumably via the portal vein. These findings were consistent with the earlier animal studies of Chaikoff's laboratory [3,4]. Since opportunities for studying chyle in the human species are rare, it is not surprising that in recent years the most productive advances in fat digestion and absorption have been made in experimental animals. Indeed, the last ten years have seen enormous progress in this field due to utilization of new analytical technics and isotopic labelling of fats, and to a new method of collecting chyle in unanesthetized animals over long periods of time [5]. An excellent review of

these advances has been written by Bergström and Borgström [6].

Recently we have had the opportunity to carry out experiments on fat absorption in an adult female patient with chyluria. Clinical aspects of this condition have been reviewed by Yamauchi [7] and by Lazarus and Marks [8]. The advantages presented by this anomaly are clear: chyle en route to the blood stream from the intestine during the course of fat absorption is shunted into the urine and is presented for study unmixed with previously absorbed fat. Moreover, this defect permits sampling of the chyle with no inconvenience to the patient. It is the purpose of this report to describe the clinical data in this patient, to discuss the nature of the anatomical defect and its eventual treatment, and to describe certain long-term studies on the absorption of various dietary fats which were carried out under rigidly controlled conditions. Experiments with isotopically labelled fats will be reported in detail elsewhere.

#### CASE REPORT

S. V., a fifty-two year old Puerto Rican married woman, was referred to the Hospital of the Rockefeller Institute by Dr. Walter Bruck (New York City) with the diagnosis of chyluria on January 9, 1956. She complained of lumpy, milky urine; this had occurred intermittently since 1938 and constantly in the year prior to admission.

She was born in Bonce, Puerto Rico, in 1903 and had lived there until she was sixteen when she moved to New York City. She remained in New York thereafter except for a visit of a few weeks' duration to San Juan, Puerto Rico, in 1936 at the age of thirty-three.

<sup>\*</sup> From the Rockefeller Institute, New York, New York. Supported in part by grants from the Swedish Medical Research Council and Eli Lilly & Co.

She was in good health until the age of thirty-five when she noticed that her urine suddenly became milky. She had noted no fever or itching of the skin prior to the occurrence of these symptoms. She was told by a physician that her condition was caused by a tropical disease, but no treatment was given. In 1941 she was admitted to a hospital in New York City for investigation, but during her stay the urine became clear and she was discharged without a definite diagnosis. Milkiness of the urine recurred shortly thereafter but disappeared during pregnancy in 1946. Thereafter her symptom-free periods became less frequent, until in the twelve months prior to admission her urine was constantly milky, and the passage of clumps produced dysuria and occasional bleeding. On arising in the morning her urine often was clear, but it invariably became milky in the late afternoon. Urinary frequency occurred only during the day. In the month prior to admission she noted generalized weakness, exertional dyspnea and dependent edema of the legs. Despite this edema there was a 15 pound weight loss during the year.

In 1950 she suffered her first attack of biliary colic. Because of recurrent attacks of pain cholecystectomy was performed in 1953; the gallbladder was enlarged and contained three large stones. Further exploration of the abdomen revealed a fibroid uterus and an esophageal hernia. Retroperitoneal exploration was not reported; routine appendectomy was performed.

Physical examination showed a well developed and nourished woman who appeared fatigued but not pallid. Her height was 165 cm., weight 61.9 kg., blood pressure 95/60 mm. Hg. The temperature, pulse and respiration were all normal. There was moderate edema of the lower legs, together with bilateral varicosities. Tender external hemorrhoids were present. The abdomen showed no abnormalities except that the musculature of the anterior wall was conspicuously flaccid. The remainder of the examination, including rectal and pelvic examinations, was negative.

X-rays of chest and abdomen showed no abnormalities of soft tissues or of bones. An intravenous pyelogram (30 per cent urokon®) was normal; neither kidney was ptotic. A Wassermann test was negative. The hemoglobin was 14.8 gm. per cent, hematocrit 44 per cent; red blood cells 4.1 million and white blood cells 5,100 per cu. mm., with a normal differential count. The erythrocyte sedimentation rate was 15 mm./hour (Westergren). A skin test for filariasis [9] was negative. No filariae were found in night blood or urine on direct smears. Electrocardiograms were repeatedly normal.

The total cholesterol was 171 mg. per 100 ml. serum, free cholesterol 41, phospholipids 186, triglycerides 94. The serum albumin was 4.3, globulins 1.1 gm. per 100 ml. The plasma sodium was 142.0, potassium 5.2, chloride 102 mEq./L.; CO<sub>2</sub> 29.5 mM./L. The urinary sodium was 105, urinary potas-

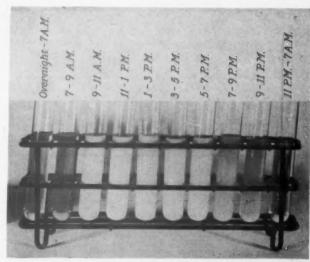


Fig. 1. Urine specimens excreted over a twenty-four-hour period at time intervals specified. Test dose of corn oil (40 gm.) emulsified in fat-free formula was administered orally at 7 A.M.

sium 20 mEq./twenty-four hours when intakes were respectively 121 and 32 mEq./day.

Urine voided in the morning was almost clear and contained only small amounts of protein and fat. On a regular ward diet, urine voided later in the day was always milky. After standing for several days in a cold room it remained homogeneous except for clots of fibrin. On a regular diet the twenty-four-hour output of urine varied from 2 to 3,000 ml.; the highest specific gravity recorded was 1.012, but this variable was not systematically studied. Microscopic examinations of the urine showed varying but small numbers of white and red blood corpuscles and no casts. Darkfield examinations were not made. The blood urea nitrogen on three occasions was 12, 16 and 9 mg. per 100 ml. Urea clearance with the patient ambulatory was 68 per cent, but this rose to 89 per cent when performed during strict bedrest; the lower figure was presumed to be due to dilution of urine urea by chyle when the patient was ambulatory.

The composition of the fat in the urine during various dietary regimens is shown in Table I. About 88 per cent of the fat was triglycerides, 10 per cent phospholipids and 2 per cent cholesterol and cholesterol esters. Of the total cholesterol, 60 to 70 per cent was esterified. On a fat-free diet the urine rapidly lost its milky color but was still opalescent and contained some protein and fat. In Figure 1 an experiment is shown in which 40 gm. of corn oil was incorporated in a fat-free diet at 7 A.M.; the urine was collected at two-hour intervals during the day. Before the feeding in the morning the urine was almost clear, but after the meal it turned milky in about two hours.

Analyses of urinary protein nitrogen excretion were carried out for several days on a fat-free diet and also after adding fat to the diet. (Table 1.) The total daily output of protein did not increase when 40 gm. of corn

TABLE I DIETARY FAT INTAKE AND URINARY FAT OUTPUT DURING METABOLIC STUDY OF PATIENT WITH CHYLURIA

		Dietary Intake	Urinary Output per 24 Hours							
Day	Basic		Total Fat Intake (gm.)	Total Fat (gm.)	Triglyc- erides* (gm.)	Phospholipids (mg.)	Cholesterol			Protein
	Diet	Test Supplement					Free (mg.)	Total (mg.)	% Esteri- fied	(gm.)
1 2 3	Ad lib.† Ad lib. Ad lib.		28 85 55	4.970 15.010 10.340	3.915 12.971 8.903	669 1546 1010	•••	272 347 301		14.2
4	Fat-free		1.5	1.229	0.888	102		168		12.6
5	Fat-free		1.5	0.621	0.395	67	***	112	**	8.4
6	Fat-free		1.5	0.942	0.671	91		127		9.7
7	Fat-free		1.5	1.601	1.124	234		171		8.6
8	Fat-free		1.5	1.481		191				11.2
9	Fat-free	Corn oil, 40 gm.	41.5	6.515	5.755	577	54	131	59	9.1
10	Fat-free		1.5	0.962	0.550	212		141		7.3
11	Fat-free		1.5	1.699	0.979	358		255		11.7
12	Fat-free		1.5	1.787	1.289	251	106	174	39	15.8
13	Fat-free	Corn oil, 40 gm. containing oleic acid-1-C <sup>13</sup> as triglyceride	41.5	9.683	9.065	219	108	282	61	13.4
14	Fat-free		1.5	1.451	1.068	158	***	159		10.4
15	Fat-free		1.5	1.422	1.012	170	70	172	59	10.9
16	Fat-free	Corn oil, 40 gm. containing oleic acid-1-C <sup>13</sup> as free acid	41.5	8.385	7.516	544	86	229	63	
17	Fat-free	***********	1.5	2.332	1.468	458	***	286	**	12.4
18	Fat-free		1.5	1.467	0.924	246		209		11.7
19	Fat-free	Corn oil, 40 gm. containing palmitic acid- 1-C <sup>12</sup> as triglyceride	41.5	9.381	8.694	354	56	222	75	****
20	Fat-free		1.5	1.708	1.059	368	69	196	65	11.4
21	Fat-free		1.5	1.411	0.874	329	54	146	63	10.4
22	Fat-free	Corn oil, 20 gm. containing palmitic acid- 1-C <sup>18</sup> as free acid	21.5	5.822	5.175	271	69	253	73	
23	Fat-free	0 - 11 - 11 20	1.5	1.542	1.010	231	:::	210	4.7	14.9
5	Fat-free Fat-free	Cs triglyceride, 20 gm.	21.5	0.559	4 050		101	121 253	17	40.0
6	Fat-free	Constant 20 cm	1.5	1.766	1.050	357	130		63	15.5
7	Fat-free	Coconut oil, 20 gm.	21.5	3.607	3.053	182	130	275	53	14.2
8	Fat-free		1.5	1.832	1.170	287 372	***	264	**	
9	Fat-free	Vesst legishin 11 am	1.5	1.871	1.084	230	224	292	25	13.9
0	Fat-free	Yeast lecithin, 11 gm.	12.5	2.598	1.945	273		242		11.4
1	Fat-free		1.5		1.189	338	71	194	64	14.0
2	Fat-free	Cholesterol, 300 mg.	1.5	1.803	1.189	140	88	274	68	
_	Fat-free	Cholesterol, 500 mg.	1.5	1.720	1.287	211	85	167	49	13.6
	Fat-free		1.5	2.467	1.740	392	69	228	70	10.9
	Fat-free	Cholesterol, 300 mg. and corn oil, 20 gm.	21.5	7.069	1.740	392	151	293	49	10.2
	Fat-free		1.5	1.907	1.352	239	45	207	78	15.3
		Two	-week Interva	al at Home	-					
4	Fat-free	Chimyl alcohol-1-C <sup>14</sup> , 25 mg. (-4 μc.) in corn oil, 2.5 gm.	4.0							

4	Fat-free	Chimyl alcohol-1-C <sup>14</sup> , 25 mg. ( $-4 \mu c$ .) in corn oil, 2.5 gm.	4.0
8	Fat-free	Cholesterol-4-C <sup>14</sup> , 8 mg. (= 20 μc.) in corn oil, 20 gm.	21.5
12	Fat-free	Cholesterol-4-C <sup>14</sup> , 8 mg. (= 20 $\mu$ c.)	1.5
15	Fat-free	Cholesterol-4-Cl <sup>4</sup> , 8 mg. (= 20 μc.) in corn oil 20 gm., with β-sitosterol, 5 gm.	26.5

\* When free cholesterol was not measured, triglycerides were calculated as explained elsewhere [22], assuming the ratio of free cholesterol to tota cholesterol to be 0.38 (the average of fifteen of the eighteen measured ratios of free to total cholesterol).

† Ad lib. diet—day 1—Calories, 898; protein = 20, fat = 28, carbohydrate = 52% of total calories.

day 2—Calories, 1,997; protein = 15, fat = 38, carbohydrate = 47% of total calories.

day 3—Calories, 1,512; protein = 15, fat = 33, carbohydrate = 52% of total calories.

‡ "Fat-free" formula (see Table 11), Calories 1,955; protein = 15, fat = 1, carbohydrate = 84% of total calories.

oil was incorporated in the diet. Zonal electrophoresis of serum and of urine on a starch-supporting medium was carried out [10] when the patient was fasting and after ingestion of corn oil. (Fig. 2.) The patterns of the protein components in serum and urine were identical

when the diet was fat-free, and were unchanged when corn oil was added to the diet.

Protamine sulfate in 10 per cent solution was added to a sample of milky urine. The fat particles immediately aggregated and floated to the surface.

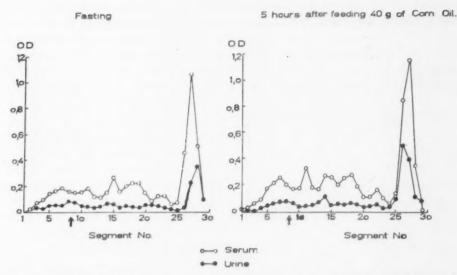


Fig. 2. Electrophoretic patterns of proteins in serum and urine before and after ingestion of test meal containing 40 gm. corn oil. The electrophoretic method of Kunkel and Slater [10] was employed.

Cystoscopy and retrograde pyelography were performed on two occasions by Dr. A. J. Paquin (New York Hospital). On the morning of the first examination the patient ate a fat-rich formula. The bladder urine was milky on initial catheterization. After the patient had been lying down for about fifteen minutes, the cystoscope was inserted easily and the bladder was washed out. No fistulous openings in the bladder were seen, and clear urine flowed from both ureters. Urine samples collected from both ureters were protein- and fat-free. Catheters passed easily to each renal pelvis. Retrograde pyelograms were normal. The cystoscope was removed and the patient permitted to walk about. The cystoscope was again inserted and a milky clot was seen to issue from the left ureteral orifice.

Nine days later a second cystoscopy and retrograde pyelography were performed, again after a breakfast rich in fat. This time the cystoscope was inserted immediately after the patient had been placed on the table. Three jets of milky fluid were seen emerging from the left ureteral orifice; thereafter the urine became clear. From the right ureter the urine was always clear. Ureteral catheters were passed to the renal pelvis on the left side, but only to one-third the vesicopelvic distance on the right. With the patient recumbent the urine collected was completely clear and protein-free on both sides. When the patient sat up the drainage from the left ureteral catheter became milky in six minutes, while that from the right ureteral catheter remained clear. Specimens were collected and the patient was asked to recline once more. In eight minutes the urine from the left side became clear again. The catheters were left in position and the cystoscope was replaced with a Foley catheter. The patient was allowed to walk about with all three catheters in place; urine was collected from both ureteral catheters as well as from the bladder. After

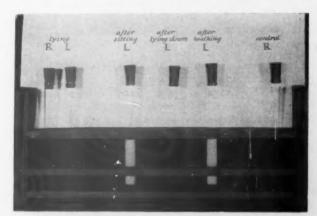


Fig. 3. Sequential urine specimens obtained during cystoscopy with patient in various positions. R and L were obtained from catheters in right and left ureters. Urine from right kidney was always clear (control – R), while urine from left kidney became creamy only with patient in upright posture.

four minutes the drainage from the left ureteral catheter became milky while that from the right side remained perfectly clear even after five minutes. (Fig. 3.) Bilateral retrograde pyelograms and cystograms again showed no abnormalities.

#### DISCUSSION OF CLINICAL ASPECTS

The diagnosis of chyluria due to anastomosis of lymphatic channels between the intestinal tract and the left renal pelvis was based on the following criteria:

1. The fat in the urine had the same composition as that described for normal human thoracic duct lymph [11,12]. The major part of the urinary fat consisted of triglycerides. Only about 10 per cent of the fat was phospholipids, 2 to 3

per cent was cholesterol. (Table 1.) Borgström [13] has recorded a similar lipid pattern in the chyle of rats.

2. There was a close relationship between ingestion of a meal high in fat and the appearance of fat in the urine. (Fig. 1.) The urine became

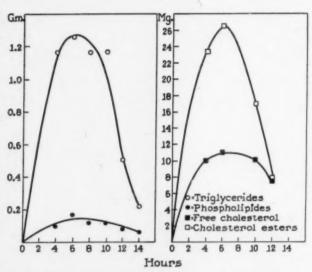


Fig. 4. Chemical analyses of urine samples obtained at intervals over a twenty-four-hour period after a test dose of 40 gm. of corn oil at 7 A.M. (same specimens as shown in Figure 1). Note difference in vertical scales in two halves of figure. During fat absorption the triglycerides of chyle increase most strikingly but other lipids also rise and peaks of all curves are simultaneous.

milky two to four hours after the test meal was eaten; the fat content reached its peak at six hours and did not decrease until after ten hours. Chemical analyses (Fig. 4) showed that the increase in urinary fat was due primarily to a rise in triglycerides. Phospholipid concentrations exceeded those of cholesterol at all times, and the changes in cholesterol occurred primarily in the ester fraction.

3. After feeding carbon-labelled lipids there was prompt appearance of the labelled compounds in the urinary fat [14].

4. The zonal electrophoretic pattern of the urinary protein was almost identical with that of the serum. Similar results in rats were obtained by Borgström and Laurell [15], in other laboratory animals by Courtice and Morris [16], and in a patient with chyluria by Löwgren [17].

5. Protamine sulphate added to the urine aggregated the chylomicrons, and the aggregated particles were readily centrifuged to the surface. This behavior, which is typical of chylomicrons but not of heavier lipoproteins, was originally described by Brown [18].

6. Cystoscopic studies demonstrated chyluria originating exclusively in the region of the left renal pelvis, but only when the patient assumed an upright position. No abnormalities could be found in the bladder or right ureteral system whether the patient was supine or upright.

The postulated communication between the left renal pelvis and the lymphatics was not visualized by pyelography. However, the close functional relationship between the intestinal lacteals and the urinary tract existed only when the patient was in the vertical position. Therefore, it is not difficult to understand why pyelography carried out with the patient supine failed to demonstrate the postulated channels. In retrospect, it would have been enlightening to have injected the contrast medium while the patient was upright.

The etiology of the condition in this patient remains obscure. It is generally believed that chyluria results when for some reason (previous trauma, retroperitoneal malignancy, filarial infection) stenosis of the thoracic duct causes dilatation of intestinal lymphatic channels and development of anastomoses with renal lymphatics. In this patient no trauma was known and a malignant process seems unlikely on the basis of the eighteen-year history of her complaint. Filariasis is not uncommon in Puerto Rico where the patient lived for sixteen years, and chyluria is not a rare complication of this disease. An absence of microfilariae in the blood and urine twenty years after her last visit to an endemic area does not rule out the possibility of an antecedent infection with this organism. Neither does a negative skin test for filariasis exclude the diagnosis, although it has been thought that the test remains positive for many years in patients infected with this parasite [19].

It was demonstrated that the posture of the patient profoundly affected the flow of intestinal lymph into the urinary tract. As in many of the cases reported in the literature [8], chyluria appeared only when the patient was out of bed. After the experiments to be described had been completed, strict bedrest was instituted for two weeks in the hope that the anastomotic channels might spontaneously close. During this time the urine was almost free of fat and protein, although the diet of natural foods was high in protein and normal in fat. During this repletion period the patient gained about 3 kg. in body weight, and her serum protein increased from 4.5 to 5.5 gm. per 100 ml. However, when she sat up after two

TABLE II
COMPOSITION OF THE "FAT-FREE" FORMULA FED DAILY AS SOLE SOURCE OF NUTRIENTS\*

Constituents	Weight (gm.)	Protein (gm.)	Fat (gm.)	Carbohydrates (gm.)	Cholesterol (mg.)	Na (mEq.)	K (mEq.)	Calories
Lesofac®†	146	74	1.5	57.4	37	1.3	32	535
Dextrose	355			355				1,420
Water	1,060							
Total	1,561	74	1.5	412.4	37	1.3	32	1,955

\* For vitamins and minerals, see text.

† A low-salt, low-fat milk protein product no longer available [21].

weeks of strict bedrest the urine immediately turned milky, indicating that the abnormal lymph channels were still patent.

Our various observations on postural effects suggested that intra-abdominal pressure might regulate the closing and opening of the lymph channels. When intra-abdominal pressure was increased by applying two abdominal binders tightly around the abdomen the urine immediately turned clear and remained free of fat and protein even while the patient was ambulatory after eating a meal rich in fat. For the last year the patient has used a tight corset whenever she was out of bed; her urine has remained almost completely clear during this entire period. She has carried on full household activities, is free of edema and appears to be in excellent physical condition.

In explanation of the success of this simple therapeutic measure we suggest that increased intra-abdominal pressure has supported the left kidney in such a manner as to occlude the fistula, but we cannot exclude the possibility that pressure per se closed the thin-walled lymphatic pathways. Whatever the exact mechanism, it is clear that lymph has been transported normally from the intestine for the last year, and that complete stenosis of the thoracic duct may have resolved. It seems probable that surgical removal of the left kidney would result in permanent relief of symptoms but the simplicity of our current medical management of her problem recommends continuance of this regimen.\*

\* Since this report was prepared, a second patient with chyluria has been studied at this hospital by Dr. M. L. Peterson. The clinical picture and cystoscopic findings made in this fifty-nine year old Puerto Rican were similar to those described herein. In addition, complete relief of chyluria was obtained by use of a tight corset.

#### FAT ABSORPTION STUDIES

Prior to the diagnostic studies described the patient was studied under metabolic ward conditions for eight weeks. Her activity was rigidly standardized during this period. She had complete bedrest from 10 p.m. to 6 a.m. and from 1 to 2 p.m., and spent the remaining hours almost entirely in sitting positions. Full lavatory privileges were permitted, as well as a minimal amount of walking on the hospital floor. These restrictions were prescribed because of the known effect of physical activity on lymph flow [8,20]. She wore loose-fitting hospital garments during the entire study period.

The patient was maintained on a regular ward diet for the first three days after admission; food intakes were calculated from standard tables. Thereafter her basic diet consisted of oral feedings of a "fat-free" formula, the composition of which is given in Table II [21]. It is noted that her dietary fat intake amounted to 1.5 gm. per day, and that this originated in the milk protein product, lesofac. She required 1,560 gm. of this formula per day (= 1,950 calories) to maintain constant body weight. Not counting urinary losses of protein and fat, her caloric requirement was 33 calories/kg. of body weight. The formula was given in six equal feedings between 7 A.M. and 10 P.M. and was supplemented at standardized intervals with a total of 2,000 ml. of water. Her daily total fluid intake was thus 3,010 ± 70 ml., and her urine output averaged 1,934 ± 300 ml. per day. In addition she was given 6 gm. sodium chloride in enteric-coated tablets (six doses) and two multivitamin capsules (unicap®\*). She received 2 gm. of methyl cellulose (melozet® wafers†) and three tablespoons of an agar preparation (metamucil®‡) each day as bulk laxatives; she required no other catharsis or enemas.

Urine collections were made in twenty-four-hour periods starting at 7 A.M. unless otherwise specified. Equal volumes of 95 per cent ethanol were added, and

<sup>\*</sup> Upjohn Co.

<sup>†</sup> Merck Sharp & Dohme.

<sup>‡</sup> G. D. Searle & Co.

the mixtures were stored at 4°c. until analyzed. Stools were collected as three- or four-day collections with carmine markers, or as individual specimens.

Administration of test fats was made by blending weighed quantities of these materials in the fat-free formula on the morning of each test. Test meals were

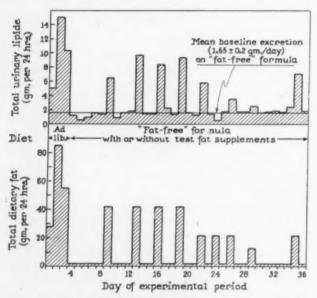


FIG. 5. Dietary intake and urinary output of fat throughout experimental period. Ad libitum diet fed for three days, thereafter fat-free formula (Table II) alone or with supplements of test fats as illustrated. Baseline excretion of fat on the fat-free formula is discussed in text.

fed at 7 a.m.; throughout the remainder of the day the fat-free formula was fed at the usual times. No correction was made for the extra calories received in test meals. Absorption studies were carried out with 20 or 40 gm. quantities of corn oil (mazola®); coconut oil; a synthetic glyceride consisting mainly of C<sub>8</sub> fatty acids; cholesterol; and yeast lecithin. Studies with isotopically labelled oleic acid, triolein, palmitic acid, tripalmitin, chimyl alcohol and cholesterol will be described elsewhere [14].

Total fat in the urine was measured by extraction of a blended aliquot with 20 volumes of 95 per cent ethanol:ether (3:1). This was followed by filtration, evaporation to 2 to 3 ml. in vacuo at lower than 30°C., and re-extraction several times with petroleum ether (b.p. 60 to 70°C.):chloroform (2:1). The rectified extract was dried over anhydrous sodium sulphate and made to volume. Aliquots were taken for determination of total and free cholesterol, phospholipid phosphorus and total lipid; triglycerides were calculated by difference and include the small amounts of nonesterified fatty acids present in chyle [14]. These methods have been described previously [22].

Protein nitrogen in the urine was determined by Kjeldahl digestion after precipitation with sodium tungstate, distillation into boric acid and back titration with hydrochlonic acid [23]. Sodium and potassium were determined by flame photometry using

lithium as internal standard. Chloride was determined by Van Slyke and Hiller's modification of Sendroy's method [24].

#### COMMENTS

The Functional Size of the Anastomotic Lymph Channels. As the data in Table 1 and Figure 5 show, the amount of lipid excreted in the urine daily was surprisingly constant when the fat-free diet was given. When 40 gm. of corn oil was fed at 7 A.M. on days 9, 13, 16, 19, the urinary lipids totalled 6.5, 9.7, 8.4 and 9.4 gm.; on the last three days the mean loss was 9.2 gm. per day. Only 20 gm. of corn oil was incorporated in the test meals on days 22 and 35, and on those days the urinary lipids equalled 5.8 and 7.1 gm. The fat-free diet was ingested on twenty-four separate days: the total urinary lipids ranged from 0.6 to 2.4 gm. Three-quarters of these observations fell in the range of 1.4 to 1.9 gm., mean 1.65, standard deviation  $\pm 0.2$ .

The excretion of 1.6 gm. per day of urinary lipid while ingesting the fat-free formula represents a baseline loss derived in part from endogenous lipoproteins originating by transudation from the intestinal blood flow. Exogenous dietary lipid also contributed to this loss since the fat-free formula contained 1.5 gm. of lipid per day's intake. After ingestion of test meals containing large loads of fat, the total urinary lipid is corrected for the baseline loss in order to estimate the magnitude of the shunt. Thus on days when 40 gm. of corn oil was ingested in addition to the fat-free formula the corrected urinary fat output averaged (9.2 - 1.6) or 7.6gm. (= 18 per cent of the intake). When 20 gm. was ingested the corrected mean output was 4.9 gm., or 23 per cent of the intake. Thus we estimate that the patient shunted about 20 per cent of her intestinal lymph into her urinary tract at this period in her course.

If it is assumed that 20 per cent of the dietary fat was shunted when the fat-free formula was fed (= 0.3 gm.), it can be calculated that (1.6-0.3) or 1.3 gm. of urinary lipid on those days was derived by transudation from blood flow to the intestine (= intestinal lymph). This in turn represented only 20 per cent of the total transuded lipoprotein lipid. Therefore  $(1.3 \times 5)$  or 6 gm. of lipoprotein lipid estimates the total amount of lipoprotein lipid transferred to the intestinal lymph from the intestinal blood per day. Since the patient's plasma lipids totalled 540 mg. per 100 ml., 6.5 gm. would have been derived from approximately 1 L. of transuded

plasma per day. While these estimates of intestinal lymph flow are admittedly crude, they are consistent with the data in human beings de-

scribed by Bierman et al. [11].

The assumption that the patient had a fairly constant baseline excretion of endogenous lymph, whether or not fat was added to the diet, is validated by the urinary protein data. (Table 1.) These outputs remained remarkably fixed from day to day, mean 11.95, standard deviation ±2.45 gm. protein per day. There was no increase in proteinuria on days 9 and 13 when 40 gm. of triglycerides were incorporated in the fat-free formula, nor was there a rise in urinary protein when as much as 85 gm. fat was included in the ad libitum diet. In short-term experiments in rats, on the other hand, meals high in fat increased the flow of lymph protein very significantly [15,25]. Possibly, the discrepancy reflects a species difference between rats and man, yet it seems more likely to be due to differences in experimental conditions. In our patient no compensary metabolic readjustments were required which could be compared to postoperative conditions in the rat experiments. Our long-term observations caused our patient no distress and were made during a metabolic steady state. The absence of any increase in urinary protein output on days when test meals included fat suggests that dietary fat per se caused no appreciable increase in blood flow through the intestine.

Absorption of Short-chain Fatty Acids. Several investigators [3,4,26] have shown in experiments on rats that fatty acids of C14 chain length and longer are transported entirely by way of the thoracic duct, while shorter acids are transported via the portal vein. Fernandes et al. [2] showed in man that C<sub>8</sub> fatty acids are not transported via the lymphatic pathway. In our patient two experiments were carried out which provide further data on this aspect of fat transport. On day 24 the patient was fed 20 gm. of a glyceride synthesized mainly from C<sub>8</sub> acid (the content of C6 and C10 acids was less than 20 per cent). No increase in urinary lipids resulted. The urine showed no turbidity at any time during the day, and indeed the total lipid in the urine (0.56 gm.) was the lowest encountered throughout the entire study. On day 26 the patient was fed 20 gm. of coconut oil, equivalent to 12.5 gm. of fatty acids of chain length longer than C12. The urinary lipid recovered that day totalled 3.6 gm. The 2.0 gm. of fat lost in the urine (corrected for baseline excretion of 1.6 gm.) was

equivalent to 16 per cent of the long-chain fatty acids ingested. In view of the correspondence between this and previous estimates of the shunt size, the data suggest that the C<sub>12</sub> and shorter acids were not absorbed via the lymphatics.

Absorption of Ingested Lecithin. On day 29 the patient's test meal included 11 gm. of yeast lecithin purified by chromatography on alumina by Hanahan [27] and kindly donated by him. Total urinary lipids were 2.6 gm., but there was no increase in urinary phospholipids. The entire increment in output over the usual baseline consisted of urinary triglycerides. Shortterm experiments in rats, utilizing isotopically labelled materials, have indicated extensive hydrolysis of phospholipids during the absorption process [28,29]. The absence of a rise in urinary phospholipids under our conditions indicates that lecithin is mainly converted to triglyceride during absorption. However, only about 10 per cent of the test dose was found in the urine rather than the 15 to 25 per cent expected, suggesting incomplete hydrolysis and/ or absorption.

Absorption of Cholesterol. Experiments in rats have shown [30] that cholesterol is transported entirely via the lymphatics, none being carried through the portal system. On days 32 and 35 cholesterol (300 mg.) was added to the formula alone and with 20 gm. of corn oil, respectively. There was no apparent increase in the output of urinary cholesterol on either day. (Table 1.) These tests merely signify that cholesterol was not rapidly absorbed from the intestine. In other experiments using isotopically tagged cholesterol [14], it was shown that exogenous cholesterol is indeed absorbed and transported via the lymphatics. The degree to which ingested cholesterol is esterified during absorption cannot be estimated accurately from the data in Table 1; this point was explored in experiments with isotopic cholesterol.

#### SUMMARY

A patient with chyluria is described in whom the defect is ascribed to a shunt between the gastrointestinal lymphatics and those of the left renal pelvis. Increasing the intra-abdominal pressure by means of a corset abolished the patient's chyluria. The diagnosis, pathogenesis and successful treatment in this case are discussed.

The patient was studied under rigidly controlled conditions for eight weeks, during which time a series of absorption experiments were conducted. About 20 per cent of the intestinal lymph was shunted into the urine. Only the long-chain fatty acids were absorbed via the lymphatic pathways. Lecithin was not absorbed as such, but only after conversion to triglycerides.

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# Acquired Fibrinogenopenia\*

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ALTHOUGH congenital fibrinogenopenia is rare, acquired fibrinogenopenia is being recognized frequently as the mechanism of a hemorrhagic disorder [1,2]. Acquired fibrinogenopenia may result from defective fibrinogen synthesis (hepatic disease, terminal malignancy), from excessive fibrinogen consumption following intravascular release of thromboplastic substances (placenta abruptio, amniotic fluid embolism, intrauterine fetal death) or it may occur in association with activation of fibrinolysins (shock; burns; neoplasms of prostate, bladder, stomach, pancreas; major pulmonary or abdominal surgery [1-4]).

This paper describes pertinent clinical and investigative findings that concerned two patients with acquired fibrinogenopenia. In each instance the coagulation defect was detected in vitro by a simple, rapid test for fibrinogen deficiency [5], and confirmed in vivo by administration of intravenous fibrinogen. The pathogenesis of the fibrinogen deficiency in these affected persons and the merits of early diagnosis in acquired

#### METHODS

fibrinogenopenia of pregnancy will be discussed.

Bleeding time was measured by Duke's technic (normal, one to four minutes), the platelets enumerated by direct count (normal 200,000 to 300,000), tourniquet test by positive pressure (normal, 0 to 5 petechiae), and clot retraction read two hours after clotting in silicone tubes (normal 3/3 or more retraction). Venous clotting times were determined in glass (normal seven to fifteen minutes) and silicone tubes (normal twenty-five to forty minutes) and plateletpoor plasma clotting times in silicone tubes (normal 1,400 to 2,400 seconds, 89 per cent plasma) using blood drawn by the two-syringe silicone technic. Mixtures of the patient's platelet-poor plasma and normal blood were studied by the method of Conley [6] for any clot-delaying activity inherent in the patient's specimen due to an abnormal anticoagulant. These mixtures were also observed after twenty-four hours' incubation at 37°c. for fibrinolysis. The one-

stage prothrombin was estimated by Quick's method (normal, twelve to fifteen seconds, 75 to 100 per cent) using whole undiluted patient's plasma, and by the Owren-Ware [7] method with addition of Ac-globulin and fibrinogen to diluted patient's plasma (normal twenty-three to twenty-eight seconds, 85 to 100 per cent). The two-stage prothrombin activity (normal 80 to 100 per cent, 300 to 360 thrombin u./ml.) and Ac-globulin activity (normal 80 to 110 per cent, 13 to 17 u./ml.) were determined by the methods of Ware and Seegers [8], and prothrombin consumption by the one-stage procedure of Stefanini [3] (normal, twenty seconds or more, 20 per cent or less residual serum prothrombin one hour after clotting). Quantitative plasma fibrinogen was assayed by the method of Ratnoff and Menzie [6] (normal, 200 to 350 mg. per cent) using a tyrosine calibration curve, and fibrinolysin by Astrup and Mullertz's fibrin plate procedure [6]. The fibrinogen titer (normal 1:100 to 1:400) was performed by a recently standardized method [5] that is a semiquantitative estimate of plasma fibrinogen content.

#### CASE REPORTS

Case I. R. R., a sixty-seven year old white man, was admitted to the Veterans Administration Hospital, Lebanon, Pennsylvania, March 18, 1955, complaining of bouts of epistaxis since December 1954, and spontaneous ecchymoses of the extremities since December 1955. The epistaxis often required nasal packing, and the cutaneous ecchymoses appeared without trauma over the arms, forearms, thighs and lower legs. His only other symptoms were those of boring, penetrating epigastric pain radiating to the back of six months' duration, and weight loss of 10 pounds in the year prior to hospitalization. The abdominal pain bore no constant relation to food or alkalis, and previous to 1954 there were no hemorrhagic phenomena.

The significant past history included onset of cough with expectoration in 1949, associated with a dense pulmonary infiltration of the left upper lobe. Although no acid-fast bacilli were found in the sputum or gastric washings, a presumptive diagnosis of pulmonary tuberculosis was made. In 1950 lobectomy of the left upper lobe was performed at another hospital; the pathologist's diagnosis was tuberculosis. In

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1951 several large left axillary lymph nodes were excised, and a histologic diagnosis of tuberculous adenitis was made. In 1952 empyema of the left pleural space developed and, after chest drainage, left thoracoplasty was performed. In the postoperative period osteomyelitis of the left index finger developed which, together with the pleural disease, responded to para-aminosalicylic acid and streptomycin therapy. The family history and system review were not relevant.

Physical examination in March 1955 revealed a thin, sixty-seven year old man weighing 121 pounds, with a long left-thoracotomy scar and thoracoplasty. The temperature, pulse and respirations were normal, the blood pressure was 130/60 mm. Hg. The skin and mucous membranes were pale. The left side of the chest was deformed, portions of the left first to ninth ribs resected, and expansion was minimal. Diminished fremitus, dullness to percussion, and diminished breath sounds were found over the left lung field due to pleural thickening. The right lung field was normal. The liver edge was 4 cm. below the right costal margin, the hepatic surface firm but not nodular. Bilateral pulmonary osteoarthropathy of the distal phalanges was evident. Many large ecchymoses were noted, in both upper and lower extremities, but there were no petechiae or hemarthroses. The remainder of the general examination, including that of rectum and prostate, was not unusual.

Initially the hemoglobin was 10.1 gm. per cent, erythrocytes 3.3 million per cu. mm., leukocytes 12,100 per cu. mm., platelets 195,000 per cu. mm., reticulocytes 0.4 per cent. During active hemorrhagic episodes, the hemoglobin later fell to as low as 5.1 gm. per cent, and erythrocytes to 1.72 million per cu. mm. During periods of bleeding, increase in band forms of neutrophils and rare normoblasts appeared in the peripheral blood. The platelets were adequate in number and of normal morphology in all blood films. Representative differential count revealed 60 per cent neutrophils, 7 per cent monocytes and 33 per cent lymphocytes. Direct antiglobulin (Coombs) test was negative. The red cell osmotic fragility was normal.

All urine specimens were abnormal. The specific gravity ranged from 1.011 to 1.014, and plus-four proteinuria was present without glycosuria. The urine sediment contained innumerable red cells during bouts of hematuria, and at other times 20 to 30 red cells, 3 to 5 leukocytes, and many granular and hyaline casts per high power field. The blood urea nitrogen was 12 mg. per cent on admission, and gradually increased to a value of 34.5 mg. per cent (63 mg. per cent non-protein nitrogen in the eleventh month of hospitalization). Total serum proteins initially were 6.7 gm. per cent, partitioned as 3.9 gm. albumin and 2.8 gm. globulin. There was a slow reduction in serum albumin during hospitalization to a level of 1.5 gm. per cent, with 2.9 gm. globulin in the eleventh month following admission.

The first strength tuberculin test was negative, the second strength test was positive. Intradermal tests with coccidiodin and histoplasmin were negative. Sputum specimens and twenty-four-hour urine concentrates disclosed no acid-fast bacilli. The blood glucose was 92 mg. per cent. Serologic tests for syphilis were non-reactive. No Bence-Jones protein was found in urine specimens. Stool specimens were positive for occult blood. The Congo red test was negative, as 61 per cent of the dye remained in the serum sixty minutes after injection. The vital capacity was 1.6 L. (41 per cent) and 1.9 L. (48 per cent) on separate occasions.

A bromsulphalein test resulted in 8.5 per cent dye remaining after forty-five minutes. The serum bilirubin was 0.26 mg. per cent, alkaline phosphatase 4.0 Bodansky units, cholesterol 270 mg. per cent, esters 50 per cent. The thymol turbidity test was reported as 2.25 units, the cephalin-flocculation test as four-plus in twenty-four hours. The serum amylase was 86 units. The coagulation data were representative of severe fibrinogen deficiency and are listed later in this paper. (Table 1.)

Roentgenogram of the chest disclosed deformity of the left hemithorax, as only the left lower three ribs remained intact. The residual portion of the left lung was well aerated, and the right lung was clear. Bone survey revealed no skeletal metastatic disease. Intravenous urogram immediately after admission resulted in prompt appearance and excretion of the dye bilaterally. Upper gastrointestinal series upon two

occasions was reported as normal.

The provisional diagnoses were: (1) arrested pulmonary tuberculosis; left upper lobe lobectomy and thoracoplasty; pulmonary osteoarthropathy, and (2) acquired fibrinogenopenia, suspected to be associated with secondary hepatic amyloidosis following chronic tuberculosis, or with carcinoma of the body of the pancreas.

The patient's clinical course in the hospital was characterized by frequent hemorrhagic incidents. Because of these and the clotting defect, bone marrow aspiration and liver biopsy were not feasible. In April 1955 frequent epistaxis was encountered, but finally arrested by nasal packing and cauterization. Later that month gross hematuria occurred, associated with right costovertebral angle pain, tenderness and fullness suggesting spontaneous right renal and perirenal bleeding. This subsided with rest, analgesics and transfusions of fresh blood, but during the hospital stay microscopic hematuria often recurred. In May 1955 a large grapefruit-sized mass, 18 × 12 cm. arose spontaneously in the soft tissue of the right chest wall. This was tender, slightly fluctuant, and believed to represent a pseudotumor due to an extensive soft tissue hematoma. It was not aspirated, and completely regressed in several weeks' time with compression bandages and transfusions. In June 1955 an accidental laceration of the left thumb bled slowly

for three days. Extensive hematomas, one within the right axilla and another in the left buttock, became secondarily infected with Staphylococcus aureus and formed large abscesses that intermittently bled and drained purulent material.

Therapy consisted of administration of fresh, whole blood, a total of thirty transfusions being given during periods of active bleeding and anemia, supplemented by 1 gm. infusions of intravenous fibrinogen. Prednisone, chiefly in dosage of 40 mg. daily, was tried with no demonstrable effect upon the fibrinogen deficit or appearance of hemorrhagic lesions. In view of the patient's previous tuberculous disease, prednisone was combined with streptomycin and isonicotinic acid therapy as a safeguard against activation of acidfast infection. Erythromycin, 800 mg./day, was effective against the staphylococcic-infected hematoma of the right axilla but without marked benefit in the treatment of the extensive gluteal abscess. Oral vitamin K, 15 mg. and ascorbic acid, 150 mg. daily, were given and a low sodium diet maintained.

Episodes of dull, penetrating mid-epigastric pain were experienced throughout the patient's hospitalization. In the sixth month of observation the liver was further enlarged to 6 cm. below the right costal margin. Hemorrhagic manifestations persisted. Pretibial edema, minimal ascites and right pleural effusion occurred, associated with decreased serum albumin. Death occurred March 17, 1956, after one years' hospitalization.

Necropsy was performed by Dr. M. Gichner, Pathologist, Veteran's Administration Hospital, Lebanon, Pennsylvania. The left lung was adherent to the lateral thoracic wall, its pleura densely thickened, and its surface fibrotic. Six-hundred cc. of amber fluid was found in the right pleural cavity, and the right lung was emphysematous. The bronchi in the lower lobe bilaterally exhibited bronchiectatic changes. The liver weighed 1,610 gm.; its gross appearance was not unusual. Five-hundred cc. of ascitic fluid was present in the peritoneal cavity.

The primary finding of the microscopic examination was the presence of amyloidosis involving the liver, spleen, pancreas, adrenals and kidneys. The liver and kidneys were principally involved. Amyloid deposits were seen within all liver lobules, underlying the sinusoidal endothelial cells. In the kidneys, the glomerular loops were universally thickened, and many glomeruli were reduced to a structureless, hyaline-like mass. Eosinophilic amyloid material created thickening of both afferent and efferent arterioles and was found in the subintima of the arterioles. Protein coagulum was found free in the lumen of many convoluted tubules. The amyloid deposits stained well with both Congo red and crystal violet.

Case II. E. H., a twenty-two year old housewife, entered the Harrisburg Hospital on September 1,

1955, in active labor. She initially presented herself at the prenatal clinic August 24, 1955, complaining of absent fetal activity for the preceding eight weeks. She was estimated to be in the twenty-fifth week of pregnancy. She had not sought obstetrical care or advice. The past medical history, system review and family history did not contain any evidence of a hemorrhagic disease in the patient or her family. In 1953 she had been delivered of a 7 pound 8 ounce infant without symptoms or signs of hemolytic disease of the newborn. Postnatally, five transfusions had been given for postpartum hemorrhage, but menstrual and hemostatic history thereafter were normal. No other pregnancies and no miscarriages had occurred.

Examination disclosed a well-nourished, twenty-two year old woman with the uterine fundus enlarged to the size of six and a half months' gestation. The temperature, pulse and respirations were normal. The blood pressure was 96/60 mm. Hg. Physical findings were not unusual, with the exception that fetal heart sounds were absent.

Admission laboratory studies showed 12.3 gm. per cent hemoglobin, erythrocytes 3.74 million per cu. mm., leukocytes 7,000 per cu. mm. with a normal differential distribution. Platelets were present in adequate number in the peripheral blood smear and were of normal morphology. A serologic test for syphilis was non-reactive. Urine examination was unremarkable. The patient's blood group was O, Rho (D) negative. The coagulation data are listed in Table 1. On roentgen examination, the pelvis contained a single fetus of about six months' gestation, breech presenting. The cranial bones were overlapping at the suture lines, with partial collapse of the calvarium. There was abnormal angulation of the fetal spine. These roentgen findings suggested intrauterine fetal death.

The patient's course during early labor was uneventful, with strong, regular uterine contractions and gradual dilatation of the cervix. After four hours' labor, in view of intrauterine fetal death, blood clotting studies were requested by the obstetrical resident, and fibrinogenopenia was demonstrated. A supply of fresh blood and fibrinogen for intravenous injection was held in readiness for use at delivery. Following five hours of labor, a macerated stillborn male fetus was delivered by frank breech presentation.

Immediately after delivery of the placenta there was massive postpartum hemorrhage, although the uterine fundus was kept firm by massage. The patient displayed pallor, perspired profusely, the pulse became rapid and thready, and the blood pressure fell to 60/38 mm. Hg. 1,500 cc. of fresh blood were transfused to correct continuing blood loss. In a separate infusion a total of 4 gm. fibrinogen was administered intravenously. Uterine hemorrhage diminished abruptly and within the succeeding two hours following such therapy vaginal bleeding was

TABLE I
LABORATORY RESULTS OF BLOOD COAGULATION STUDIES

Data	Case 1	Case II	Normal .
Bleeding time	6 minutes *	Not performed	1 to 4 minutes
Platelet count		180,000	200,000 to 300,000
Tourniquet test		Not performed	0 to 5 petechiae
Clot retraction		Determination impossi- ble, venous blood incoagulable	3% retracted, 2 hours
Venous clotting time	17 minutes (glass) * 55 minutes (silicone) *	Incoagulable *	7 to 15 minutes 25 to 40 minutes
Platelet-poor plasma clotting time		Not performed	1400 to 2400 seconds
Clot-delaying effect, platelet-poor plasma	None	Not performed	None
Fibrinolytic effect, platelet-poor plasma	None	Not performed	None
One-stage prothrombin (Quick)	46.6% (20 seconds)*	21% (31 seconds)*	75 to 100% (12 to 15 seconds)
One-stage prothrombin (Owren-Ware)	100% (22 seconds)	85% (25 seconds)	85 to 100% (23 to 28 seconds)
Two-stage prothrombin	92%	Not performed	80 to 100% (300 to 600 u./ml.)
Ac-globulin titer	55%*	Not performed	80-110% (13 to 17 u./ml.)
Prothrombin consumption	serum prothrombin	Not performed	20% or less residual serum prothrombin
Fibrinogen	35 mg. %*	15 mg. % *	200 to 350 mg. %
Fibrinolysins		Not performed	Not increased
Fibrinogen titer	1:20 dilution*	1:1 dilution*	1:100 to 1:400

<sup>\*</sup> Abnormal values

minimal, the patient responsive, and the blood pressure 108/60 mm. Hg. The remainder of the post-partum period was not unusual. Tests of the maternal serum for hyperimmune antibodies of isoimmunization of pregnancy were not made during hospitalization, through oversight, although anti-D sensitization was suspected as the cause of the fetal death. Following dismissal from the hospital, attempts to locate the patient were unsuccessful as she left the community.

### INVESTIGATION OF THE FIBRINOGENOPENIC DEFECT

In Case 1 there was opportunity for detailed investigation of intravascular coagulation in a lengthy and unremittent hemorrhagic disease. Tests were conducted when the patient had required no transfusions or fibrinogen for at least one week. In Case 11 the hemostatic disorder was acute and self-limited, so that less extensive, but conclusive, study was possible. The results in each patient are summarized in Table 1.

In the first patient fibrinogenopenia was suggested by increased bleeding time, minimal delay in the venous clotting time, and a prolonged one-stage whole plasma prothrombin

time (Quick's method). Alexander [2] has directed attention to the one-stage whole plasma prothrombin time as a screening procedure for significant fibrinogenopenia, stating that this activated plasma clotting time lengthens as the plasma fibrinogen falls progressively below 100 mg. per cent. One-stage plasma prothrombin procedures in which prothrombin-free plasma, containing Ac-globulin and fibrinogen, is added to the patient's plasma (Owren-Ware [7]) result in normal values when hypofibrinogenemic plasma is tested. This, together with a normal two-stage quantitative prothrombin, aids in distinguishing the fibrinogenopenic defect from true prothrombin deficiency, as is well demonstrated in the tabulated results in both patients. A prolonged bleeding time may occur if a decreased amount of fibrinogen is available in the formation of the hemostatic plug. Venous clotting times will be prolonged in proportion to the severity of the fibrinogen deficiency. Thus in the second patient a greater diminution in plasma fibrinogen resulted in incoagulable venous blood.

In each patient the most direct and rapid con-

firmation of fibrinogenopenia as the primary clotting defect was obtained by titering the plasma fibrinogen. Since normal values for this assay range from 1:100 to 1:400 [5], results of 1:20 and 1:1 dilutions, respectively, suggested levels of fibrinogen within the hemorrhagic

TABLE II
ACQUIRED FIBRINOGENOPENIA OF PREGNANCY

During Postpartum Hemorrhage	After IV Fibrinogen (4 gm.)
Incoagulable	21 minutes 20 sec- onds (silicone)
21% (31 seconds)	100% (15 seconds)
1:1 dilution	1:100 dilution
	Postpartum Hemorrhage  Incoagulable  21% (31 seconds)

zone—below 100 mg. per cent. This was verified later by quantitative fibrinogen determination, a more accurate although time-consuming procedure. The first patient also exhibited moderate Ac-globulin deficiency, which was not unexpected in view of the progressive hepatic amyloidosis which probably disturbed synthesis of this protein as well as that of fibrinogen and serum albumin. A hemorrhagic diathesis is not experienced usually unless Ac-globulin levels of 25 per cent activity or less occur. Thus lack of proaccelerin was not considered to play a significant role in this patient's hemorrhagic disease.

Taken together, the in vitro tests in each of these two patients gave clear evidence of fibrinogenopenia as the basic mechanism of the hemorrhagic state. In vivo confirmation of this diagnosis was obtained by the response to intravenous fibrinogen. Rapid administration of purified human fibrinogen (4 gm.) was needed to arrest brisk postpartum hemorrhage in the second patient. Two hours after fibrinogen infusion, the venous clotting time, one-stage whole plasma prothrombin time, and fibrinogen titer reverted to normal, as shown in Table II. This could be attributed only to correction of the acquired fibrinogenopenia and was coincident with clinical cessation of bleeding. All measures of coagulation remained normal subsequently.

The first patient was studied at a time when transfusions were not required for ten days. The venous clotting time (silicone), quantitative fibrinogen, and fibrinogen titers were measured

before and serially after an infusion of intravenous fibrinogen. (Table III.) Since endogenous fibrinogen synthesis was minimal, these observations provided rough measures of the survival of administered fibrinogen in the patient's circulation. Maximum improvement occurred

Table III
ACQUIRED FIBRINOGENOPENIA OF HEPATIC DISEASE
(EFFECT OF 1 GM. FIBRINOGEN INFUSION)

Time of Test	Venous Clotting Time (Sili- cone) (min.)	Quantitative Fibrinogen (mg. %)	Fibrino- gen Titer
Pre-injection	42	35	1:20
2 hours postinjection	26	75	1:50
4 hours postinjection		68	1:50
24 hours postinjection		55	1:20
48 hours postinjection		60	1:20

two hours postinjection, with acceleration of the venous clotting time and a rise in both quantitative fibrinogen and fibrinogen titer.

Although 1 gm. of parenteral fibrinogen was not sufficient to increase the plasma fibrinogen above the critical hemorrhagic level of 100 mg. per cent, a modest increase was demonstrable as long as forty-eight hours. Immunochemical technic employed to follow the survival of intravenous fibrinogen in patients with congenital afibrinogenemia [9] demonstrated a maximum elevation of plasma fibrinogen within forty-eight hours after the fibrinogen transfusion. However, one-half of the administered fibrinogen disappeared extravascularly during this first forty-eight hours, and thereafter the disappearance of fibrinogen followed a logarithmic decay curve with a half-life of four days. This is in close agreement with the half-life of 5.6 days for fibrinogen estimated from radioisotope turnover studies [10].

More graphic evidence of a specifically improved coagulation system in this first patient was obtained by observation of the venous blood clots prior to and following intravenous fibrinogen. Before fibrinogen injection the patient's clot rapidly liquefied within thirty minutes after its formation, resembling sedimenting blood drawn in an anticoagulant solution. (Fig. 1.) Even upon tilting this tube, no definite clot was visible. When this liquid venous specimen was

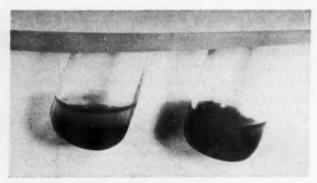
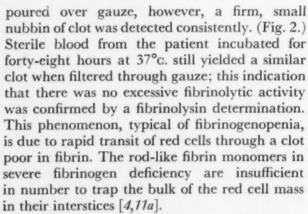


Fig. 1. Left, liquid venous blood before injection of fibrinogen. No clot is visible by gross inspection. Right, visible clot after 1 gm. intravenous fibrinogen.



After intravenous fibrinogen, a firmer clot resulted that was not subject to dissolution. (Fig. 1.) This clot, similarly poured onto gauze, was of greater size and strength when compared to the pretherapy specimen (Fig. 2), and furnished visual proof of proper diagnosis and specific in vivo correction of the patient's disorder.

#### COMMENTS

The factors believed to induce acquired fibrinogenopenia are discussed amply in the literature [1-3,4], and are listed briefly in the introduction to this article. In the first patient there was no demonstrated excessive fibrinolytic activity and no disseminated fibrin emboli were discovered at postmortem examination to suggest increased fibrinogen consumption. Faulty hepatic production of fibrinogen associated with amyloid disease would explain the hemorrhagic disorder in this instance. Hepatic amyloidosis as a cause of fibrinogenopenia has apparently not been reported previously. Other forms of severe parenchymal liver disease, such as cirrhosis or acute hepatitis, are more common causes.

Acquired fibrinogenopenia of pregnancy, affecting the second patient described in this

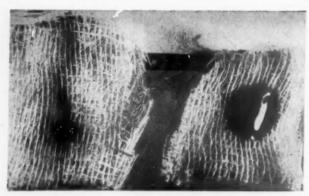


Fig. 2. Left, clot content of liquid venous blood before use of fibrinogen. Note the small clot nubbin trapped upon gauze. Right, larger, firmer clot after injection of 1 gm. intravenous fibrinogen.

paper, probably evolves through a different pathogenesis. Here tissue thromboplastic materials derived from the placenta, amniotic fluid or fetus may enter the maternal blood stream [11,12]. Triggered by such thromboplastins, intravascular coagulation ensues with formation of fibrin emboli. This process, which Schneider terms defibrination [12], may deplete the blood of its fibrinogen until hemorrhagic levels of fibrinogenopenia below 100 mg. per cent result. Fibrinolysis thereafter can rapidly remove the fibrin occlusions. Defibrination is abrupt in fibrinogenopenia associated with premature separation of the placenta and amniotic fluid embolism, so that opportunity for its detection prior to labor is minimal.

The situation is different in the fibrinogenopenic syndrome occurring with intrauterine fetal death. Hypofibrinogenemia has not been reported until five weeks or more after apparent fetal death [11] and in such patients studied by Ratnoff [11,13] fibrinogen deficiency was present for several weeks prior to delivery. His findings suggest that in this circumstance fibrinogenopenia does not develop acutely, but that maternal fibrinogen concentrations decrease gradually, and an incipient hemorrhagic state is so induced.

This sequence should persuade the physician to estimate the plasma fibrinogen content regularly in every maternity patient who experiences intrauterine fetal death of five or more weeks' duration. Had this policy been pursued in the second patient, whose clinical history listed absent fetal activity for eight weeks, it is likely that the hemostatic defect would have been discovered before labor. Either serial quantitative plasma fibrinogen values or the plasma fibrinogen titer (as its acceptable and less com-

plex substitute) could serve in the prophylactic demonstration of this variety of acquired fibrinogenopenia.

Therapy in individuals with acquired fibrinogenopenia involves both replacement of the fibrinogen deficit and removal of existing sources of abnormal tissue thromboplastins that may be entering the patient's circulation. The latter is accomplished by prompt evacuation from the uterus of the placenta with its retroplacental hematoma in the case of abruptio, or of a retained non-viable fetus. The usual 500 ml. of ACD blood contains some 0.6 to 0.8 gm. fibrinogen and this may provide sufficient substitution therapy in patient it a mild hemorrhagic diathesis. Otherwise gm. units of purified human fibrinogen, or fraction I of Cohn, may be employed.

The data in Table III suggest that when profound fibrinogen depletion occurs, with levels below 100 mg. per cent, 2 gm. of intravenous fibrinogen is about the minimal initial amount of this agent required for optimal hemostasis. If abnormal defibrination is the cause of fibrinogenopenia, a larger quantity of from 6 to 12 gm. fibrinogen may be necessary.

The response to such substitution therapy and the need for additional parenteral fibrinogen may be judged by following such parameters as the venous clotting time, one-stage prothrombin activity, and particularly the quantitative fibrinogen or fibrinogen titer determinations. In acquired fibrinogenopenia due to chronic hepatic disease, the use of intravenous fibrinogen is reserved for episodes of emergency bleeding. Too frequent and injudicious administration might result in isosensitization of the patient to exogenous sources of this vital protein substance.

#### SUMMARY

Two cases of acquired fibrinogenopenia are recorded. In one instance this blood coagulation

abnormality was associated with amyloidosis of the liver, in the other with pregnancy and intrauterine fetal death.

A simplified scheme for obtaining in vitro and in vivo evidence of severe fibringen deficiency is presented.

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## Essential Cryoglobulinemia\*

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The phenomenon of precipitation of a serum protein by cold was first thoroughly investigated by Lerner and Watson and the term cryoglobulinemia was introduced by them [1]. Recent reports [2–5] have adequately reviewed the literature and have stressed that while cryoglobulinemia is most commonly associated with a primary process, e.g., multiple myeloma, chronic lymphatic leukemia or subacute bacterial endocarditis, it sometimes occurs without any recognisable disease entity, and there has been termed essential cryoglobulinemia [2].

Of late, disorders associated with abnormal proteins have been intensively studied and this has resulted in a wider recognition of such as a purpura hyperglobulinemica, macroglobulinemia and cryoglobulinemia, and in the discovery of "cryofibrinogenemia" [4,6,7]. One clinical feature all these disorders may have in common is the presence of a bleeding tendency which is often purpuric in nature. This report concerns a patient with essential cryoglobulinemia who presented with purpura and who has been studied in some detail.

#### CASE REPORT

The patient is a forty-eight year old white man whose family and environmental history are noncontributory. Apart from frequent attacks of hives (unrelated to cold), three bouts of pneumonia many years ago and low back pain for some years, he had enjoyed good health until 1952 when his ankles began to ache and swell at the end of the day. Late in 1953 he first noticed some red spots which came in crops on his legs and inner sides of his thighs, and more rarely on his arms and chest. The spots varied in size from a pin point to a few millimeters in diameter and changed in colour over a period of a few days from red to purple and finally brown. These spots have occurred sporadically ever since and have left a permanent brown pigmentation on his legs but not elsewhere. At the time of onset of the purpura he also had intermittent attacks of night sweats, but his appetite was good

and he lost no weight. The night sweats lasted for a year and then disappeared and have not returned. In January 1956 an excruciatingly painful ulcer appeared over the left external malleolus which persisted for a year before responding to treatment. In April 1956 he had a "gangrenous" appendix removed. The operation was uneventful and there was no postoperative bleeding. In September 1956, he had some nausea with vomiting which lasted for a few days, and x-ray examination revealed a gastric ulcer, which healed rapidly with therapy. He has recently had several teeth extracted without any excessive bleeding. He cannot relate any of his attacks of purpura or the onset of his leg ulcer to exposure to cold and he had not taken cold fluids immediately prior to the development of his gastric ulcer. He has had no Raynaud's attacks but recently his feet have felt much colder.

Physical examination revealed a sallow complexioned man whose legs were wasted and bore patchily distributed confluent areas of old ecchymoses. Over the left external malleolus was a small circular ulcer approximately ½ inch in diameter. Areas of recent small hemorrhages were present on the inner sides of both thighs. The Hess test was negative, and no bone tenderness, lymphadenopathy, hepatomegaly or splenomegaly could be detected. His blood pressure was 110/90 mm. Hg. There were no varicose veins and although neither anterior tibial arteries could be elicited the remaining arterial pulses were normally palpable. Both feet felt cooler than normal. There was no ankle edema, the ocular fundi were normal and normal findings were present in all other systems. The urinary analysis: specific gravity 1.006, alkaline, no sugar or albumin and no Bence Jones protein was detected.

Laboratory studies revealed a faintly positive Sia test and the presence of a serum cryoglobulin; no pyroglobulins were detected. Cold agglutinins were absent; Paul-Bunnell test was negative; Coombs' test direct and indirect was negative; L.E. cells were not found; Wassermann and Kline tests were negative; total serum protein (Kjeldahl) was 9.0 gm. per cent; total serum protein after cryoglobulin extraction was 8.1 gm. per cent; thymol flocculation test was normal; zinc sulphate was 12 units (normal = 6 units); serum

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bilirubin was 0.4 mg./100 ml.; serum alkaline phosphatase was 6 King-Armstrong units/100 ml.; serum cholesterol was 160 mg./100 ml.; blood urea was 27 mg./100 ml.; blood uric acid was 4.4 mg./100 ml.; and blood group was A Rh positive. Other relevant findings were, hemoglobin 14.1 gm. per cent, normal red cell indices; white cell count 7,500 per cu. mm. with a normal differential count; platelets 270,000 per cu. mm., erythrocyte sedimentation rate (Wintrobe) 14 mm./hour. Erythrocyte sedimentation rates (Wintrobe) determined at 4°c., 33°c. and 37°c. were 2 mm./hour, 18 mm./hour and 25 mm./hour, respectively. Results of coagulation studies are recorded in Table I. X-rays of skull, chest and lumbar and thoracic spines were normal (Dr. A. R. Colwell).

A week later a sternal aspiration was performed and was reported as showing no significant deviation from normal (Dr. H. Kronenberg). However, on review, extensive vacuoles were noted in the cytoplasm of the plasma cells which were present in normal numbers.

#### METHODS OF STUDY

Samples of the patient's blood were collected by venepuncture using paraffined syringes, needles and test tubes heated to 38°c. The test tubes containing whole blood were placed in an incubator at 37°c. and, following clot retraction, the serum was separated by centrifuging at 37°c. Oxalated and heparinised specimens were collected in the same manner except that the plasma was separated immediately after collection by centrifuging at 37°c.

A cold precipitable globulin was looked for in the patient's serum, oxalated plasma and heparinised plasma by placing 1 ml. of each into separate Lee and White coagulation tubes and standing overnight at 4°c.

The temperature at which the cryoglobulin commenced to precipitate was determined by standing Lee and White tubes each containing 1 ml. of the patient's serum in constant temperature baths at varying temperature.

Serum cryoglobulin was extracted by centrifuging at 6°c. for one hour at 4,000 r.p.m. The supernatant serum was then removed and the precipitate washed with cold isotonic saline and centrifuged three times before suspension in normal saline. Plasma cryoglobulin was extracted and resuspended in a similar manner.

Paper electrophoresis was performed using Whatman No. 1 paper between siliconed glass plates and a veronal/veronal buffer pH 8.6, ionic strength 0.05. The dried paper was stained for protein with bromphenol blue and the periodic acid-Schiff carbohydrate stain [8] and Sudan black lipid stain [9] were used where indicated.

Ouchterlony's method of gel-diffusion [10] was employed to study the immunological properties of the isolated cryoglobulin. Purified agar (supplied by

Davis Gelatine (Australia) Pty. Ltd.) was made up to a concentration of 1.5 per cent W/V with isotonic saline, merthiolate to a final concentration of 1/10,000 was added as a preservative and the hot agar solution was poured into Petri dishes 9 cm. in diameter. Shallow cups were made in the centre of each dish so

Table 1
COAGULATION STUDIES\*

Coagulation time (Lee and White)	10 minutes (normal)			
Bleeding time (Duke)				
Clot retraction	Normal			
Platelet count	270,000/cu. mm.			
Prothrombin consumption test	41 seconds after 1 hour			
(modified Quick)	(normal)			
Before Extraction of Co	ryoglobulin			
Prothrombin time	18 seconds			
(Quick)	$(n = 17 \text{ sec.})$			
Thromboplastin generation	Normal			
Fibrinogen level	320 mg. %			
Fibrinolysin				
After Extraction of Cr	yoglobulin			
Prothrombin time	17 seconds			
(Quick)				
Thromboplastin generation	Normal			
Fibrinogen level	100 mg. %			
Fibrinolysin				

The thromboplastin generation test was performed by the method of Douglas and Biggs, 1953 using the patient's platelets.

Fibrinogen levels were determined by the method of Quick, 1951.

The Macfarlane Dilution Test [13] was used to detect fibrinolysis.

that the nearest edges were 1.2 cm. from the others at the apices of an equilateral triangle. Rabbit antiserums against a cryoglobulin, Bence Jones protein, and various fractions of human serum had previously been prepared by the technic of Kabat and Mayer [11]. A rabbit antiserum was also prepared against the patient's cryoglobulin using the same method.

Alpha<sub>2</sub>, beta and gamma globulins were obtained by eluting with isotonic saline the appropriately identified zones of paper electrophoretograms of normal serum [12].

Routine coagulation studies were first performed on the patient's whole blood, serum and plasma in the standard manner. The prothrombin time, thromboplastin generation test, fibrinogen level and modified Macfarlane dilution test [13] were then repeated using patient's plasma and serum from which the cryoglobulin had been precipitated. (Table 1.)

The patient's urine was examined for Bence Jones protein using a Bence Jones antiserum by the method of Collier and Jackson [14].

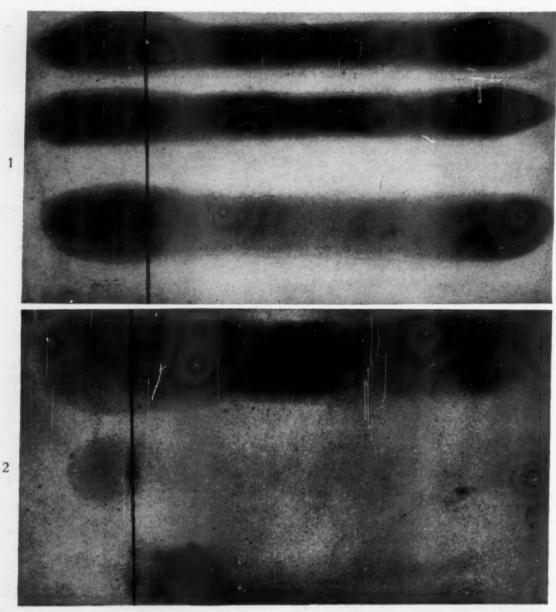


Fig. 1. Electrophoretic patterns of the patient's serum stained with bromphenol blue. At the top is the patient's whole serum, next the patient's serum following extraction of the cryoglobulin and at the bottom is the unwashed extracted cryoglobulin.

Fig. 2. Electrophoretic patterns stained with periodic acid-Schiff carbohydrate stain. At the top is the patient's whole serum, next the patient's isolated washed cryoglobulin and at the bottom is a cryoglobulin isolated from another patient.

#### RESULTS

Properties of Cryoglobulin. The cold precipitable globulin formed as a fine white sediment when the patient's serum or plasma (oxalated or heparinised) was kept at temperatures of 31°c. or lower. Equal quantities precipitated from serum and plasma but at the higher temperatures less occurred. The precipitated cryoglobulin could be completely redissolved by warming the serum or plasma to 37°c. and shaking, whether it had been formed at 4°c. or at

31°c. Examination of the precipitate under a microscope revealed amorphous material, and its appearance was the same regardless of the temperature of precipitation. The precipitate was not completely soluble in saline at 37°c. since a few flakes of sediment were left undissolved. The Sia test [4] performed with the patient's whole serum was faintly positive at temperatures ranging from 4°c. to 60°c. but was negative when the patient's serum was used after extraction of cryoglobulin. The faint positive reaction was due

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Fig. 3. Electrophoretic pattern stained with bromphenol blue. The upper pattern is the patient's whole plasma, note fibrinogen spot just in front of the starting line. The lower pattern is unwashed extracted plasma cryoglobulin, note the spot on the starting boundary which may be due to precipitated fibrinogen and compare this pattern with that of unwashed serum cryoglobulin. (Fig. 1.)

to the cryoglobulin but was independent of its thermal properties.

Electrophoresis. Paper electrophoresis of the patient's serum revealed an increased gamma globulin component when stained for protein (Fig. 1) but carbohydrate and lipid patterns were normal. The isolated cryoglobulin reacted similarly to gamma globulin when stained for protein, fat or carbohydrate and had the same electrophoretic mobility as gamma globulin. (Fig. 2.) Electrophoresis of unwashed extracted plasma cryoglobulin showed a precipitate at the starting boundary which was not present in the case of unwashed extracted serum cryoglobulin. (Figs. 1 and 3.) This precipitate was thought to be due to a fibrinogen-cryoglobulin complex since it was noted that fibrinogen migrated in front of the starting boundary when the patient's whole plasma was subjected to electrophoresis. (Fig. 3.)

Gel Diffusion. The patient's cryoglobulin was found to react in an immunologically identical manner with normal gamma globulin. It was also compared with a cryoglobulin isolated from another patient using an antiserum prepared against the latter cryoglobulin. (Fig. 4A.) The antiserum was placed in cup 1, the patient's cryoglobulin in cup 2 and the antiserum's antigen cryoglobulin in cup 3. Two closely adjacent lines of precipitate were formed with the patient's cryoglobulin and three lines of precipitate with its own specific antigen. One of the latter was well developed and eventually crossed through the bands between cups 1 and 2, showing no immunological relationship whilst the remaining two bands were very faint and are not shown

in the figure. After some days one of these faint bands showed a reaction of identity with the band closer to cup 1, between cups 1 and 2. (Fig. 4A.) This antigen common to both cryoglobulins was due to gamma globulin. (Fig. 4B.)

The patient's isolated cryoglobulin was then studied using its own specific antiserum and this showed that the cryoglobulin possessed two antigens which showed a reaction of identity with gamma globulin and therefore the antigenic properties of the cryoglobulin were similar to normal gamma globulin. (Fig. 4B.) The patient's cryoglobulin therefore appeared to be immunologically identical to gamma globulin.

No Bence Jones protein was detected in the patient's urine using anti-Bence Jones serum.

Coagulation Studies. The results of the coagulation studies are presented in Table 1. These were normal apart from the marked reduction in fibrinogen following the extraction of the cryoglobulin. This reduction was verified simply, by setting up two test tubes each containing 10 ml. of normal saline. To one was added .5 ml. of patient's whole plasma and to the other .5 ml. of the patient's plasma after the cryoglobulin was extracted. Three drops of topical thrombin (10 units/ml.) were added to each tube and the size of the fibrin clots was compared. The clot formed by the whole plasma was much larger than that by the extracted plasma. (Fig. 5.)

#### COMMENT

The acquired dysproteinemias may be regarded as belonging to the same broad group of disorders which include myeloma at one end of the scale and benign hyperglobulinemia at the

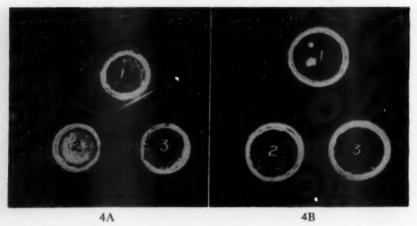


Fig. 4. A, cup 1 contains anticryoglobulin serum. Cup 2 contains patient's isolated cryoglobulin. Cup 3 contains cryoglobulin from another patient which was used to produce the anticryoglobulin serum. Two distinct bands are visible, one between cups 1 and 2 and the other between cups 1 and 3. These bands eventually crossed through one another and are therefore unrelated immunologically (Oudin [70]). A fainter band (not seen in this picture) also developed between cups 2 and 3 and this band eventually joined the one between cups 1 and 2 and showed a reaction of identity. B, cup 1 contains anticryoglobulin. Cup 2 contains patient's isolated cryoglobulin. Cup 3 contains eluted gamma globulin. Two closely adjacent bands formed between cups 1 and 2 and also between cups 1 and 3. These bands showed a reaction of identity and were therefore immunologically identical (Oudin [70]).



Fig. 5. Right hand tube contains patient's whole plasma diluted with saline and clotted with thrombin. Left hand tube contains patient's plasma from which the cryoglobulin has been extracted but otherwise treated in a similar manner. Note the reduced size of the clot in the tube containing the extracted plasma.

other, just as the myeloproliferative disorders range from leukemia to polycythemia and the reticuloses from lymphosarcoma to follicular

lymphoblastoma. The diagnostic features of the dysproteinemias have been recently reviewed [4,6]. The history and clinical findings of this patient reveal the difficulties in arriving at a correct diagnosis in these disorders. When he was first seen it was suspected from the nature of the purpura and the normal platelet count that the condition may have been due to an underlying dysproteinemia or leukemia and this was supported by the discovery of the cryoglobulin. The history of low back pain and the raised erythrocyte sedimentation rate in the absence of splenomegaly and lymphadenopathy suggested the diagnosis of multiple myeloma. The lack of any evidence from radiological, electrophoretic or bone marrow investigations together with the inability to demonstrate Bence Jones protein either chemically or immunologically appears to rule out this diagnosis. The Sia test has been suggested by Waldenström [6] as a simple screening test for macroglobulinemia although it is recognised that false positive and negative results may occur. In this patient it was faintly positive and was shown to be due to the cryoglobulin (vide supra), but the slightly raised erythrocyte sedimentation rate and the bone marrow findings together with the history and physical examination make the diagnosis of macroglobulinemia unlikely. The presence of similar amounts of cold precipitable globulin in both the patient's serum and plasma excluded the possibility of cryofibrinogenemia. As no

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evidence of any underlying disorder could be detected it was concluded that the patient had "essential" cryoglobulinemia. The unusual features in this man were the absence of any history of cold precipitating his purpuric eruptions and the latter's occurrence in areas which are normally warmer than other portions of the body. These apparent anomalies may be explained by the fact that the cryoglobulin was precipitated at temperatures well above room temperature. However, it has recently been observed that fresh eruptions have occurred on his thigh unaccompanied by changes lower down. While this may be due to the support of recently acquired elastic stockings it appears more likely that the lesions in the groins are etiologically different from those lower down, especially as the former are initially raised and red becoming brown and flat and finally disappearing entirely, whereas the latter are at first flat and red and leave a permanent brown pigmentation. This might suggest that the lesions in the groins are purely vascular while those lower down result from extravasation of blood into the tissues. The purpuric manifestations in this patient resembled those seen in another man with macroglobulinemia. The spots were rarely the size of petechiae seen in thrombocytopenic purpura, but were usually a millimeter or more in diameter. This type of eruption together with permanent pigmentation should always suggest the possibility of a dysproteinemia, especially if the Hess test is negative.

The absence of any history of his symptoms or signs being brought about or exaggerated by exposure to cold emphasises the importance of a routine examination for cryoglobulins in all patients with obscure bleeding disorders.

Electrophoretic studies showed his cryoglobulin to be similar to normal gamma globulin in composition and electrophoretic mobility, unlike another cryoglobulin studied which had a high glycoprotein content similar to that seen in multiple myeloma and a mobility of a beta globulin. (Fig. 2.)

Gel diffusion revealed that cryoglobulin was immunologically identical with gamma globulin and that this was the only antigenic property that it shared in common with another cryoglobulin previously studied.

One can only speculate as to the cellular origin of the cryoglobulin in this patient, especially as the site of origin of normal body proteins is still disputed. The plasma cells in the sternal smear were normal in number but their cytoplasm contained numerous vacuoles. This has been noted in another patient with essential cryoglobulinemia [15] and it has been suggested that these vacuoles may represent inclusion bodies of the abnormal protein which have been dissolved out with inappropriate fixative [16].

The demonstration of the adsorption of coagulation factors onto the abnormal protein in patients with dysproteinemias has raised new possibilities in the explanation of bleeding diatheses in these disorders [17]. Coagulation studies performed on the patient's serum and plasma before and after extraction of cryoglobulin are shown in Table 1. The only abnormality was a marked reduction of the fibrinogen level from 320 mg. per cent to 100 mg. per cent following the extraction of the cryoglobulin. (Fig. 5.) It was also found that when serum crycglobulin was added to normal plasma and suspended for one hour at 37°c, and then extracted there was a drop in the fibrinogen level from 250 mg. per cent to 170 mg. per cent. This diminution of its ability to absorb fibringen following extraction and washing is probably due to a physicochemical change induced by this process. Electrophoretic studies suggested that the adsorbed fibrinogen existed as an electrophoretically inert precipitate. (Fig. 3.)

Furthermore addition of topical thrombin to varying concentrations of plasma cryoglobulin in saline failed to produce fibrin formation. The sequence of events causing the purpura in this patient is postulated to be as follows. First the skin is cooled to less than 31°c. causing precipitation of the cryoglobulin which causes adsorption and inactivation of fibrinogen locally. This is followed by damage to the vessel wall by the precipitate and this, in combination with a local fibrinogenopenia, results in a hemorrhagic eruption. The importance of prior precipitation of the cryoglobulin in producing the hemorrhage is emphasised by the clinical story of our patient, since he had had an appendectomy and several teeth extracted well after the onset of his purpura, and although no special precautions were taken hemostasis was normal.

Further investigation of bleeding tendencies in patients with abnormal proteins, e.g. multiple myeloma, especially when no deficiency in a known coagulation factor can be detected, may reveal such a deficiency only after the removal of the abnormal protein. The coagulation factors adsorbed may vary depending on the physico-

chemical properties of the particular protein. The macroglobulins have been compared with barium sulphate in their ability to adsorb factors concerned with prothrombin conversion [17], while the cryoglobulin studied may be compared with dextran in its capacity to adsorb fibrinogen [18].

#### SUMMARY AND CONCLUSIONS

A case of essential cryoglobulinemia is described. The electrophoretic and immunological properties of the cryoglobulin are described and discussed and a mechanism for the patient's purpura is suggested in view of the clinical features and the results of the coagulation studies.

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## Cushing's Syndrome and Bronchogenic Carcinoma\*

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In 1952 Thorne reported two cases of Cushing's syndrome associated with bronchogenic carcinoma of the oat cell variety [1], and noted one such case in the literature [2]. Since 1952 three additional cases have been described [3-5]. We have studied a patient with both Cushing's syndrome and oat cell bronchogenic carcinoma who represents the seventh recorded example of this association, suggesting that the combination constitutes a rare but distinct clinical entity.

#### CASE REPORT

E. R. (G. U. H. No. 44869). A twenty-two year old white man was admitted to Georgetown University Hospital on December 15, 1952 with chief complaints of cough and chest pain of three and one-half months' duration. Two months before hospitalization orthopnea and night sweats had occurred, and the cough had become productive of approximately one-half cup of white mucoid sputum daily. Three weeks prior to admission he had noted mild edema of his face, ankles and knees, as well as urinary frequency and nocturia. A chest x-ray at this time had demonstrated atelectasis of the right upper lobe. Four days before admission he had coughed up about a cupful of bright red blood; small amounts of blood were coughed up daily until admission. He had gained 14 pounds despite progressive weakness, malaise and

Pertinent information in his past history included severe pertussis at age four which had left him mentally retarded and rendered him incapable of coherent speech until age eighteen. He had complained of transient scotomas for the past two years, and defective hearing of the right ear for one year. He drank alcohol in moderation, and had smoked two packs of cigarettes daily for seven or eight years. The family history was negative for cancer and otherwise non-contributory.

Physical examination on admission revealed a husky, young man sitting up in bed, coughing almost continuously. The blood pressure was 160/114 mm. Hg, the pulse rate 88, the temperature 99°F., and the respiratory rate was 24/minute. Physical findings

included an erythematous maculopapular rash symmetrically distributed over the forehead, malar regions and back; defective air conduction of the right ear; bronchial breath sounds with expiratory rhonchi and wheezes over the posterior one-third of the right upper lung field; and a smooth non-tender hepatomegaly extending below the right costal margin. Negative findings of importance included normal eyegrounds, a negative cardiac examination and no lymphadenopathy.

The hemoglobin was 15.0 gm. per cent, the hematocrit 45 per cent, and the corrected sedimentation rate (Westergren) 11 mm. in one hour. The white blood cell count was 18,050 per cu. mm. with 84 per cent mature polymorphonuclears, 4 per cent bands, 10 per cent lymphocytes and 2 per cent monocytes. The total eosinophil count was 14/cu. mm. The urine had a specific gravity of 1.010 and a pH of 6.0; there was a trace of albumin, and 5 to 6 white cells were found in each high power field. The serum non-protein nitrogen was normal. Serum protein totaled 6.6 gm. per 100 ml. of blood, with albumin of 3.8 gm. and globulin of 2.8 gm. Sputum culture showed hemolytic streptococcus and Neisseria catarrhalis. The serologic test for syphilis was negative. Urine culture revealed Aerobacter aerogenes and Pseudomonas aeruginosa. Chest x-rays showed incomplete atelectasis of the right upper lobe and enlarged hilar glands on the right side. Six twenty-four-hour sputums examined for tubercle bacilli by smear, culture and cell block were negative, as was the tuberculin skin test. Bronchoscopy revealed inflammatory changes of the right main stem bronchus with pus coming from the right upper lobe and right middle lobe bronchi; washings revealed no tubercle bacilli and the cellblock was negative. Bone marrow was non-specific in appearance; smear and cultures were negative.

Immediate treatment consisted of neo-penil,<sup>®</sup> 1,000,000 units a day, and aerosol therapy followed by postural drainage. No clinical or radiological improvement resulted, and the patient continued to expectorate large amounts of purulent material and occasional gross blood. On the twentieth day the facial rash was noted to be acneform. Neo-penil dosage was decreased and terramycin<sup>®</sup> added. Rectal tem-

<sup>\*</sup> From the Department of Medicine, Georgetown University Medical Center, Washington, D. C. This study was supported by the William Wade Hinshaw Cancer Research Fund.



Fig. 1. Photograph taken during the fifth week of hospitalization.

peratures were normal, and white counts varied between 11,000 and 20,000 per cu. mm., with a shift to the left. Renal function was normal, as measured by concentration tests, phenolsulfonphthalein excretion and intravenous and retrograde pyelograms. Cold pressor and sodium amytal tests were negative.

On the twenty-sixth hospital day a urine specimen showed 4-plus glycosuria; the fasting blood sugar was 267 mg. The serum non-protein nitrogen was 36 mg., and albuminuria and glycosuria persisted. His insulin requirements, starting with 10 units of NPH iletin, rose rapidly to 35 units, but complete control of the diabetes was never obtained. Liver biopsy specimen was reported as presenting "fatty metamorphosis"; liver function tests were within normal limits. A muscle biopsy specimen revealed normal muscle and blood vessels. Several electrocardiograms showed changes of left ventricular hypertrophy. An L.E. preparation was negative.



Fig. 2. Photograph taken during the fifth week of hospitalization.

During the fifth hospital week, wasting of the extremities was first noted. Photographic comparison with pictures taken ten months before revealed changes suggestive of Cushing's syndrome, i.e., rounding of the face, skin rash and wasting of the extremities. (Figs. 1 and 2.) Eight total eosinophil counts were all below 3 cu. mm. At this time the serum values, in mEq./L. were CO<sub>2</sub>, 33; chloride, 96; potassium, 2.9; and sodium, 147. X-rays of the spine and hands revealed no abnormalities. Clinically the course was progressively downward; the patient became stuporous, uncommunicative and incontinent of urine and feces. A lumbar puncture revealed 44 white blood cells, and a protein of 81 mg. Neurologic examination at the time was normal. During the five weeks in the hospital there had been a 40 pound weight loss, which was confined almost exclusively to the limbs, sparing the face, trunk and abdomen. On the forty-seventh day he had severe epistaxis with a drop in blood pressure from the usual value of 170/105 to 118/105 mm. Hg; thereafter the blood pressure remained below 130 systolic. During the seventh week the diabetes steadily increased in severity, requiring 30 units of regular insulin administered three times a day. At that time the urinary 17-ketosteroids excretion was 22 mg. in twenty-four hours.

On the fifty-sixth hospital day an irregular, nodular epigastric subcutaneous mass was palpated, lying superficial to the enlarged liver. A biopsy specimen showed mycelial organisms. On the sixty-third day an exploratory laparotomy was performed. The liver was found to be studded with white nodules



Fig. 3. Adrenals, showing bilateral hypertrophy and a large metastasis on the right side.

0.5 to 1.0 cm. in diameter. Both adrenals were firm and considerably enlarged. The periaortic lymph nodes were hard and enlarged. The operative diagnosis was extensive carcinomatosis from an unknown primary site, and the surgical procedure was confined to biopsy of one of the hepatic nodules. Postoperatively, the patient did well during the first few days and remained afebrile. On the ninth postoperative day his temperature rose for the first time to 102.6° F., the blood pressure dropped gradually to values of 70/40 mm. Hg, with no response to levarterenol. He became dyspneic, hyporeflexic, unresponsive, and died on his seventy-second day of hospitalization.

At autopsy, the right lung weighed 900 gm., the upper lobe was completely atelectatic, pale purple and had a meaty feel. The terminal bronchi were filled with purulent material, and throughout this lobe there were several small masses containing inspissated pus and necrotic material. The right upper lobe main bronchus presented a 4 mm. irregular firm whitish mass arising in the mucous membrane, infiltrating the wall and involving the peribronchial lymph nodes. The lower lobe was hypocrepitant, congested and showed numerous nodules. The left lung weighed 1,000 gm., was markedly congested and also contained numerous masses with pus and necrotic material. The hilar lymph nodes were hard and gritty and demonstrated numerous areas of necrosis. The heart weighed 380 gm. The liver was enlarged, weighing 2,750 gm., and contained numerous round, whitish nodules, the largest measuring 7.5 cm. in diameter. The gallbladder was normal and the biliary tree patent, with enlarged lymph nodes surrounding the common duct, upper duodenum and pancreas. The right adrenal weighed 57 gm., was hypertrophied

and contained in the lower pole a round and whitish firm mass 4 cm. in diameter. The left adrenal was grossly hypertrophied, weigning 29 gm., with cortical thickening. (Fig. 3.) The thyroid was diffusely enlarged. The testicles were small and atrophic, and the prostate was small and firm. The pancreas, the kidneys and the spleen were normal on gross examination. Permission for examination of the head was denied.

On microscopic section the lung showed pulmonary edema, bronchopneumonia and a highly anaplastic (oat cell) bronchogenic carcinoma with metastasis to the mediastinal lymph nodes. (Fig. 4.) There were also multiple mycotic abscesses in the lungs. The thyroid revealed colloid goiter and abscesses containing mycelial elements. In the liver, the nodular lesions proved to be metastatic from the lung and the rest of the parenchyma showed chronic passive congestion. The pancreas revealed moderate fatty degeneration. The adrenals presented a thin atrophic zona glomerulosa and marked hyperplasia of the zona fasciculata. (Fig. 5.) The medulla appeared intact. There was one metastatic nodule in the right adrenal cortex with the same type of cells encountered in the lung.

Summary: While hospitalized for an apparent respiratory disease, the typical characteristics of Cushing's syndrome developed in a rapidly progressive course. Although his symptom-complex on admission involved mainly the lungs, a 14-pound weight gain, in the presence of what appeared to be a severe infection, and elevation of blood pressure may well have been the initial manifestations of the endocrine disturbance. At

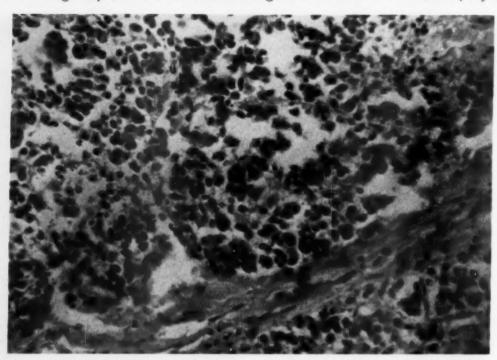


Fig. 4. Microphotograph of the bronchogenic carcinoma, original magnification × 210.

a later date, a change in the nature of the skin rash, the appearance of glycosuria and hyperglycemia, and a weight loss selectively sparing his face, thorax and abdomen, were even more suggestive of hyperactive adrenocortical function. Persistent eosinopenia, hypokalemia, and moderate elevation of the 17-ketosteroids were additional features indicative of Cushing's syndrome.

#### REVIEW OF REPORTED CASES

The association of Cushing's syndrome with tumors of various organs has been reported to include pancreatic, thymic, ovarian and bronchogenic neoplasms. The present review concerns only the association with bronchogenic carcinoma.

The first case, reported by Brown [2] in 1928, was that of a forty-five year old woman with symptoms of thirst, weakness, a sinking sensation of the stomach, obesity, hypertension, diabetes, hirsutism, purpura, and a red blood cell count of 5,700,000 per cu. mm., who died of heart failure after a downward course of several months. The postmortem findings included bilateral enlargement of the adrenal cortex and medulla, pyelonephritis, fatty changes in the pancreas, a "large" pituitary and an oat cell carcinoma of the lung 1 cm. in diameter.

Thorne reported two cases [1]. The first was that of a thirty-six year old man with pain in the

right axilla for three months, polyuria for six weeks, exertional dyspnea, cough, rapid increase in weight of 21 pounds, swelling of the abdomen, weakness of the legs, rounding of the face, and loss of scalp hair. Examination disclosed localized obesity of the face, shoulders and abdomen with wasting of the extremities, a plethoric face, numerous bruises and petechiae, purplish abdominal striae, a blood pressure of 160-180 systolic and 110-120 diastolic, diminished expansion of the right upper part of the chest, and hepatomegaly. The red blood cells were 5,200,000 per cu. mm., the hemoglobin 102 per cent, and the blood urea nitrogen 35 mg./ 100 ml. The urinary 17-ketosteroid excretion was 24.3 mg. and 17 mg. in twenty-four hours. Chest film showed fracture of three ribs and osteoporosis of the vertebrae and ribs. The pituitary fossa was radiated and there was temporary improvement. On readmission, the urinary 17-ketosteroids were 28.7 mg. in twentyfour hours and a liver biopsy specimen revealed cells suggestive of an oat cell carcinoma. Autopsy showed an anaplastic oat cell carcinoma of the left lower lobe bronchus with metastases to the regional lymph nodes and liver, and bilateral pyelonephritis. The adrenals and pituitary showed no abnormalities.

The second case reported by Thorne was a forty-five year old man with swelling of the ankles and abdomen, increase in weight (amount

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not specified), tight and smooth skin, fatigue and dyspnea. Examination showed sparsity of body and scalp hairs, red abdominal striae, sacral edema, blood pressure of 220/130 mm. Hg, and hepatomegaly. There was an opacity of the right lower lung on x-ray but no osteoporosis. The red blood cell count was 5,900,000 per cu. mm., the hemoglobin 115 per cent, and the blood urea nitrogen was 31 mg. per cent. He had a diabetic glucose tolerance test and persistent glycosuria. The serum sodium was 147; the CO<sub>2</sub>, 32; and the chlorides, 99 mEq./L. The urinary reducing steroids were 8.2 mg. and later 5.6 mg. (normal, 0.2 to 0.4), and the 17-ketosteroids 29.2 mg. in twenty-four hours. The patient became drowsy and jaundiced, and died after a total course of fourteen months. Autopsy showed an oat cell carcinoma of the right lower lobe bronchus with lymphadenopathy; an abscess of the left lower lobe; necrotic areas in the tail of pancreas; metastases to the liver, adrenals and posterior pituitary; and marked adrenal hyperplasia. No abnormalities were found in the anterior lobe of the pituitary.

The fourth reported case [3] concerned a seventy-six year old white woman with a tenyear history of mild heart failure and a recent history of progressive weakness, dyspnea, anorexia, polyuria, facial hirsutism and a receding hairline. Physical examination revealed a moderately obese woman with a round, florid and hirsute face, who was blind in the left eye. There was periorbital fullness; questionable signs of ascites; a tender and enlarged liver; edema of the hands, forearms, lower extremities and abdomen; and twitching of the jaw and left leg. The blood pressure was 170/100 mm. Hg. The urine contained albumin and glucose. The red blood cell count was 4,120,000 per cu. mm., and the total eosinophil count was zero. The serum electrolytes, in mEq./L., were: potassium, 3; sodium, 138.7; chloride, 90; CO<sub>2</sub>, 40.7. The fasting blood sugar was 317 mg.; non-protein nitrogen, 36 mg.; calcium, 7.8 mg.; and phosphorus, 3 mg./100 ml. of blood. The serum proteins were 4.3 gm. per cent, the bromsulphalein® retention was 42 per cent, and the blood pH, 7.55. Chest x-ray showed obliteration of the left costophrenic sulcus and a 3 cm. diameter density of the right apex. One determination of the urinary 17-ketosteroids showed 43.2 in twenty-four hours. The course was rapidly downward. Autopsy revealed an oat cell carcinoma of the right upper lobe bronchus with

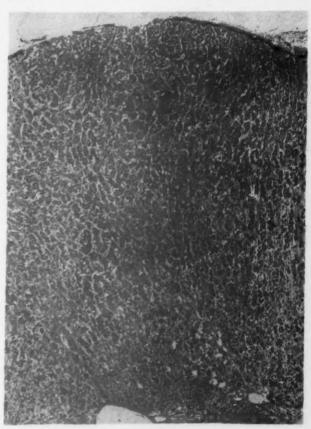


Fig. 5. Microphotograph of the adrenal cortex demonstrating hyperplasia and a small mitotic lesion, original magnification × 21.

metastases to the posterior pituitary, the interventricular septum of heart, the fundus of the gallbladder, the pancreas and the right ovary; mild nephrosclerosis; and acute pancreatitis with fatty necrosis. The adrenals weighed 38 gm. and had a nodular surface. There was hyperplasia, mainly of the zona fasciculata and reticularis, and atrophy of the zona glomerulosa. The anterior pituitary showed an increase in the hyaline and sparsely granulated basophils and the hypertrophic amphophils noted in adrenal hyperactivity.

A probable fifth case was reported as "diabetes insipidus associated with edema" [4]. A fifty-eight year old man gave a recent history of right-sided headaches, intense polydipsia, 25 to 30 pound weight loss, productive cough, dyspnea, swelling of the ankles and hyperpigmented skin. The patient appeared lethargic and dehydrated. His lungs contained scattered rales and wheezes; the liver was enlarged and described as hard and non-tender; the blood pressure was 140/72 mm. Hg. The hemoglobin was 14.9 gm. per cent; blood sugar, 140 mg.

per cent; CO<sub>2</sub> combining power, 36; chlorides, 104; sodium, 164; and potassium, 3 mEq./L. The average daily urinary excretion of 17-ketosteroids was 30.5 mg. Bromsulphalein retention was 24 per cent. X-ray showed a pulmonary soft tissue density localized in the posterior part of the thorax. The patient became massively edematous, and studies showed that he retained ingested sodium, and excreted large quantities of potassium. On the fifteenth hospital day acute pulmonary edema developed. The patient went into shock, and died the next day. Autopsy disclosed a primary bronchogenic carcinoma in the left hilar region, infiltrating the left lower bronchus, which proved to be an undifferentiated anaplastic type of carcinoma. There were metastases to the liver, adrenal cortex and medulla, duodenum, frontal lobe of the brain and posterior pituitary lobe. The adrenals showed cortical hyperplasia.

A sixth case report [5] concerned a fifty-six year old man whose symptoms began two weeks before admission to the hospital, with irritability and fatigue. Later there was fever and perspiration, diarrhea and drowsiness. On admission, he was obese, drowsy and dehydrated. The face was flushed and cyanotic; the blood pressure was 130/70 mm. Hg. There was glycosuria and hyperglycemia. The CO2 combining power was 97 volumes per cent. The serum sodium was 146; the chloride, 75; and the potassium, 2.5 mEq./L. Total eosinophil counts were 11 and 44 cu. ml., urinary excretion of 17-ketosteroids varied between 11.3 mg. and 46.9 mg. per twenty-four hours, "corticoids" from 8.1 mg. and 13.7 mg. per twenty-four hours, and 11oxysteroids between 4.2 mg. and 7.9 mg. in twenty-four hours. An intravenous pyelogram showed a downward displacement of the left kidney by a mass thought to be an adrenal tumor. Chest x-ray disclosed a small, oval density extending above the left hilum. Resection of the left adrenal tumor, 9 by 6.5 by 2.5 cm., was performed. This proved to be a metastatic, anaplastic tumor, thought to have originated in the lung. The patient died on the fourth postoperative day. Autopsy revealed a grayish mass at the left pulmonary hilum with neoplastic tissue extending to the upper lobe, and causing narrowing of the bronchus. There were metastases to the mediastinal lymph nodes, the liver and the enlarged right adrenal. Microscopic examination of the tumor revealed spindleshaped (oat) cells.

In addition to these six cases, Cope and Raker [6] have referred to two other patients presenting the association of bronchogenic cancer and Cushing's syndrome [7,8].\*

#### COMMENTS

Analysis of the reported cases brings out several points. Many of the patients either gained weight or maintained a stationary weight in the presence of a rapidly spreading carcinomatosis. There were frequent references to the obesity or edema in these patients. Our patient was of interest in that following an initial weight gain of 14 pounds he began to lose weight as his condition deteriorated, but the loss was noticeable mostly over his extremities and spared the face, thorax and abdomen. Weight gain or edema may have represented an underlying hyperadrenocortical state in the face of a history pointing to severe pulmonary disease, with or without other suggestive elements for Cushing's syndrome. Along the same lines the acute nature of the onset of features of adrenal cortical activity should be emphasized. In the reported cases rapid development of Cushingoid features was impressive and in the case reported herein such rapid development was an outstanding feature.

In the four reported cases in which electrolyte determinations were made, as in our case, the changes characteristic of hypokalemic alkalosis were present. (Table 1.) In the other two cases polydipsia or polyuria was noted which, although possibly the result of diabetes, might have been associated with hypokalemic nephropathy. Hypokalemia, with associated elevation of bicarbonate and depression of chloride, has been observed in uncomplicated Cushing's syndrome in a small percentage of cases [9]. Thorne has called attention to the fact that this electrolyte distortion is particularly frequent when Cushing's syndrome is associated with thymic tumors, an association which has close similarity, both clinically and histologically, to bronchogenic carcinoma with adrenal hyperfunction [1]. The unusually high incidence of this electrolyte abnormality suggests the production of excessive aldosterone secretion but permits no ready explanation for the relative infrequency of alkalosis in uncomplicated adrenal hyperfunction. In three of the patients with the

<sup>\*</sup> Another patient with Cushing's syndrome and carcinoma of the lung mentioned by Cope and Raker is the one reported in [3].

Table I
PERTINENT FEATURES OF REPORTED CASES OF CUSHING'S SYNDROME WITH
BRONCHOGENIC CANCER

	Age	34037	Serum Electrolytes (mEq./L.)				Weight	Adrenal		
Reference	(yr.)		Na	K	Cl	CO <sub>2</sub>	Edema	Gain	Metastases	Miscellaneou
Brown [2]	45	F	****				?	?	No	Polydipsia
Thorne [1]	36	M					Yes	Yes	No	Polyuria
	45	M	147.0		99.0	32.0	Yes	Yes	Yes	
M. G. H. [3]	76	F	138.7	3.0	90.0	40.7	Yes	No	No	Polyuria
White [4]	58	M	164.0	3.0	104.0	36.0	Yes	Yes	Yes	Polydipsia
Spaulding [5]	56	·M	146.0	2.5	75.0	44.0	No	?	Yes	
Present case	22	M	147.0	2.9	96.0	33.0	Yes	Yes	Yes	

triad of Cushing's syndrome, bronchogenic carcinoma and hypokalemic alkalosis, there were metastases to the hyperplastic adrenal; in a fourth case with equally prominent electrolyte disturbances there were none. Obviously the presence of low potassium, elevated bicarbonate and depressed chloride in instances of Cushing's syndrome should stimulate consideration of coexisting carcinoma, particularly the bronchogenic variety.

The rapidly fatal course was another characteristic feature of the cases reviewed. Other authors have suggested that the hyperadrenocortical state may have contributed to the rapidly fatal course and wide metastases. The mortality figures in untreated Cushing's syndrome have varied with different series but most authors agree that in about 50 per cent of the cases the patients have a better than five-year survival [10]; therefore, it is safe to state that the natural history of Cushing's syndrome was sharply abbreviated by its association with the bronchogenic carcinoma. The reverse statement, namely that the course of the lung neoplasm probably was accelerated by adrenocortical hyperfunction, may also be applicable in at least five of the seven cases.

We can offer no data suggestive of any physiopathologic mechanism linking these two conditions. It is impossible to establish conclusively which appeared first and therefore to establish a cause and effect relationship based on chronology. The youth of the patient reported here suggests that the adrenal overactivity may have stimulated development of cancer at an unduly early age. Other reported cases, however, were at or near the age when pulmonary malignancy is more frequent. There is no evidence to support the idea that tumors other than of the pituitary or the adrenal cortex can secrete a substance which might produce the clinical aspects of Cushing's syndrome. By the same token, one has to rule out the questionable explanation that cancer and Cushing's syndrome may both be manifestations of some other, unknown, causative agent.

The question whether carcinomas can be due to, or their spread enhanced by, adrenocortical hormones is controversial. Experimental data show that cortisone may promote growth of transplanted sarcomas in animals [11]. However, as far as we know, there have been no cases in which adrenal or pituitary hormones were definitely implicated as the etiologic agents of neoplastic processes. A bit of suggestive evidence linking steroid hormones to cancer is provided by Dobriner and his associates [12]. High levels of urinary excretion of delta-9-etiocholanolone were found in the majority of prostatic carcinomas as well as in a few other neoplasms that were studied (breast and larynx as well as in leukemia). Elevation of this metabolite was also noted in five of seven instances of Cushing's syndrome, and in three of six hypertensive patients, while twenty-two of twenty-four apparently normal subjects failed to excrete this substance in the urine. However, these data, stimulating as they appear to be, do not permit one to draw any more definite conclusion about the mechanism linking bronchogenic carcinoma and Cushing's syndrome. Another possible explanation that could be invoked is that neoplasia may act as stressful agents and produce the release of ACTH by the anterior pituitary. If this were so, one would expect that the features of adrenal hyperfunction would be more

frequently associated with neoplasia.

It appears that the association of the two conditions herewith presented constitutes a clinical entity beyond the realm of mere coincidence. Although no statistical data are available regarding the incidence of Cushing's syndrome in the general population, we may reason that the likelihood of such a rare entity as Cushing's syndrome in association with bronchogenic carcinoma in at least seven known cases is highly improbable on the basis of chance. Moreover, it seems definitely beyond mere chance distribution that all seven cases presented the same histological type, the anaplastic variety of carcinoma in which the cells are described as spindle or oat cell in appearance. The significance of the association of Cushing's syndrome with this particular type of cancer is emphasized by the fact that in a large series of cases of bronchogenic carcinoma the incidence of the oat cell variety was only 9 per cent [13]. It is likely that the final answer concerning exact mechanisms linking bronchogenic tumor and Cushing's syndrome may be directly related to the histological type of this neoplasm.

#### SUMMARY

The clinical and pathological features of a case illustrating the combination of Cushing's syndrome and bronchogenic carcinoma are presented. Six patients with a similar syndrome have been reported and two others have been mentioned in the medical literature. All seven patients had the same histological type of pulmonary lesion, an undifferentiated (oat cell) carcinoma, and demonstrated adrenal hyperplasia.

The clinical pattern of this combination of disorders includes three significant features: (1) weight gain or maintenance of normal weight in the presence of rapidly progressive carcinoma; (2) acute development of features of adrenal hyperfunction; and (3) a rapidly fatal course. Hypokalemic, hypochloremic alkalosis appears

to be a frequent component of this syndrome, as contrasted with its relative rarity in uncomplicated Cushing's syndrome.

The incidence of the association of these two relatively rare diseases appears to exceed mere chance occurrence but no explanation can be advanced concerning possible cause and effect relationships. The association of Cushing's syndrome due to adrenal hyperplasia and undifferentiated bronchogenic carcinoma appears to constitute a distinct syndrome.

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PREMENSTRUAL TENSION

DYSMENORRHEA

MENORRHAGIA

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METRORRHAGIA

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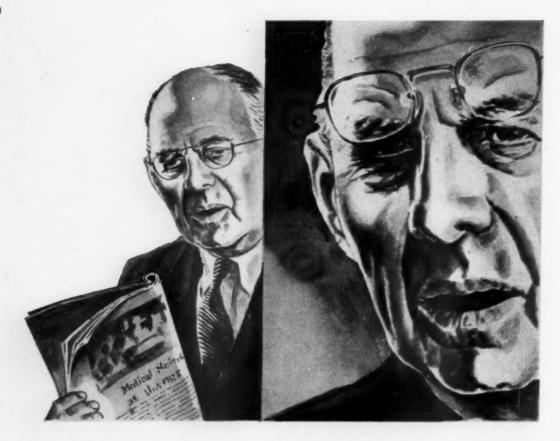
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1. Bendig, A.: New York State J. M. 66:2523, 1956. 2. La Barbera, J. F.: Med. Rec. and Ann. S0:242, 1956. 3. Glichrist, A. R.: Brit. M. J. No. II:1011, 1956.

A new concept in antihypertensive therapy: concomitant use of an improved ganglionic blocking agent ('Inversine') and a new antihypertensive agent ('Diuril') for smoother, simplified management of hypertension

# Longer Life for Hypertensives

In moderate, severe, and malignant hypertension, ganglionic blocking 'Inversine' often makes possible a lessening of cardiovascular-renal damage, regression of the basic disease, and prolongation of life.

"When employed under carefully controlled conditions with adequate attention to proper regulation of dosage, mecamylamine ['Inversine'] may be expected to reduce blood pressure effectively and to ameliorate various manifestations of hypertensive-cardiovascular disease. These include such symptoms as headache, dizziness and vertigo, hypertensive encephalopathy and cerebral or subarachnoid hemorrhage, retinopathy, cardiac hypertrophy, and, in some cases, cardiac decompensation."

Council on Pharmacy and Chemistry, New and Nonofficial Remedies: Mecamylamine Hydrochloride, J.A.M.A. 162: 1469-1471, Dec. 15, 1956.

Now, concomitant use of a newly discovered antihypertensive agent ('Diuril') has been found to enhance the hypotensive effect of 'Inversine'—while reducing the required dosage of 'Inversine' and often minimizing the serious side effects of ganglionic blockade.

#### 'Inversine'

MECAMYLAMINE HYDROCHLORIDE

#### a greatly improved ganglionic blocking agent

Unlike the other ganglionic blocking agents, 'Inversine' is not a quaternary ammonium compound. It is a secondary amine, and has significant advantages over all other ganglionic blocking drugs:

- of the orally effective blocking agents, only 'Inversine' is completely and uniformly absorbed
- it provides predictable, reproducible effects with minimal day-to-day fluctuations in blood pressure response
- 'Inversine' is effective in low dosage
- permits convenient dosage schedules
- · usefulness not limited by development of tolerance
- it has a gradual onset of effect, reducing the likelihood of sudden drops in blood pressure

#### 'Diuril'

CHLOROTHIAZIDE

#### new and unique antihypertensive agent

- provides basic therapy to improve and simplify the management of hypertension
- often reduces dosage requirement of ganglionic blocking agents and other antihypertensive agents below the level of serious side effects
- added to other antihypertensive agents, is often effective in controlling blood pressure of even highly resistant cases
- smooths out blood pressure fluctuations
- effectiveness not diminished by development of tolerance
- well tolerated even at maximum therapeutic doses

#### DOSAGE RECOMMENDATIONS

#### New Patients

1. Initiate 'Diuril' therapy

'Diuril' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. Add 'Inversine' as follows:

('Inversine' is established in the same manner whether used with 'Diuril' or alone.) Recommended initial dosage is 2.5 mg. 'Inversine' twice a day, preferably after meals. May be increased by 2.5 mg. at intervals of no less than two days until desired response is obtained. In severe or urgent cases, the increments may have to be larger or more frequent, with the largest dose given preferably at noon or in the evening. 'Inversine' is extremely potent and should always be titrated according to the patient's orthostatic blood pressure response.

3. Adjust dosage of 'Diuril' for optimal response.

Patients on 'Inversine' and/or other ganglionic blocking agents

1. Initiate 'Diuril' therapy

'Diuril' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. Adjust dosage of ganglionic blocking agent

If the patient is established on a ganglionic blocking agent (e.g., 'Inversine') it should be continued, but the total daily dosage should *immediately* be reduced by as much as 25 to 50 per cent. This will reduce the serious side effects often observed with ganglionic blockade.

If other antihypertensive agents are used, their dosage should be adjusted as indicated by patient response.

3. Determine optimal maintenance dosage

The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

PRECAUTIONS: Side effects of 'Inversine' are essentially the same as those encountered with other ganglionic blocking agents. At the first sign of constipation, vigorous treatment must be initiated immediately since paralytic ileus may result if constipation is unchecked. Patients should be informed how to cope with postural hypotension should this occur. 'Inversine' is contraindicated in coronary insufficiency, organic pyloric stenosis and recent myocardial infarction.

SUPPLIED: 'Inversine', tablets of 2.5 mg. and 10 mg. Bottles of 100. 'Diuril', tablets of 250 mg. and 500 mg. Bottles of 100 and 1000.

## Inversine MECAMYLAMINE HYDROCHLORIDE

Diuril

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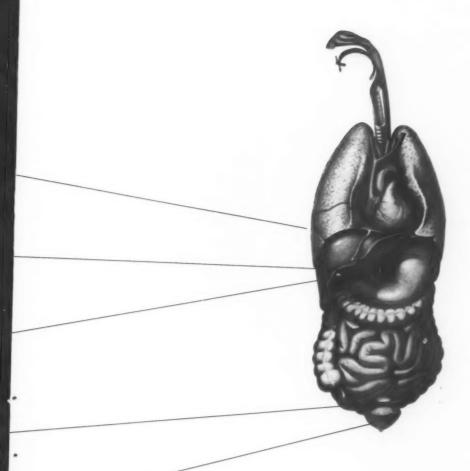
0.88 mcg./ml.<sup>1</sup> (at 10 hrs. after 500 mg. dose)

urine

50.3 mcg./ml.<sup>3</sup> (av. concentration following 500 mg. dose)

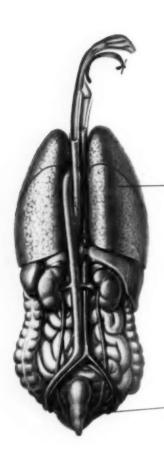
1. Shidlovsky, B. A., et al.: In Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 459
2. Pulaski, E. J., and Isokane, R. K.: Antibiotic Med. 4:408, 1957.
3. Buckwalter, F. H., and Cronk, G. A.: Ibid. 5:46, 1958.





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1. Cronk, G. A., et al.: In Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 397. 2. Rein, C. R., and Fleischmajer, R.: Antibiotic Med. 4:422, 1957. 3. Putnam, L. E.: Ibid. 4:470, 1957. 4. Prigot, A., et al.: Ibid. 4:287, 1957. 5. Council on Drugs, A.M.A.: J.A.M.A. 166:50, 1958. 6. Shidlovsky, B. A., et al.: In Antibiotics Annual 1957-1958, vide supra., p. 459.

#### Investigator

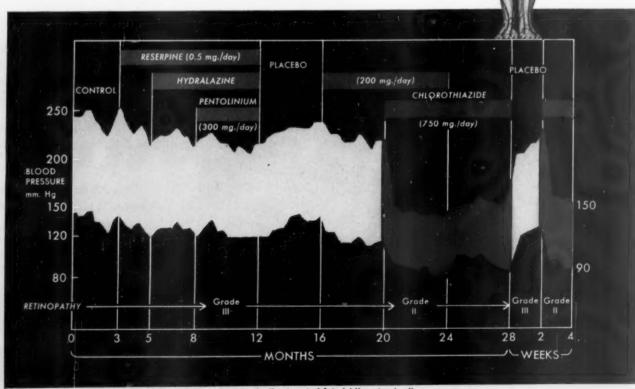
#### after investigator reports

Wilkins, R. W.: New England J. Med. 257:1026, Nov. 21, 1957.

"Chlorothiazide added to other antihypertensive drugs reduced the blood pressure in 19 of 23 hypertensive patients." "All of 11 hypertension subjects in whom splanchnicectomy had been performed had a striking blood pressure response to oral administration of chlorothiazide." "... it is not hypotensive in normotensive patients with congestive heart failure, in whom it is markedly diuretic; it is hypotensive in both compensated and decompensated hypertensive patients (in the former without congestive heart failure, it is not markedly diuretic, whereas in the latter in congestive heart failure, it is markedly diuretic). . . .

Freis, E. D., Wanko, A., Wilson, I. H. and Parrish, A. E.: J.A.M.A. 166:137, Jan. 11, 1958.

"Chlorothiazide (maintenance dose, 0.5 Gm. twice daily) added to the regimen of 73 ambulatory hypertensive patients who were receiving other antihypertensive drugs as well caused an additional reduction [16%] of blood pressure." "The advantages of chlorothiazide were (1) significant antihypertensive effect in a high percentage of patients, particularly when combined with other agents, (2) absence of significant side effects or toxicity in the dosages used, (3) absence of tolerance (at least thus far), and (4) effectiveness with simple 'rule of thumb' oral dosage schedules."



In "Chlorothiazide: A New Type of Drug for the Treatment of Arterial Hypertension," Hollander, W. and Wilkins, R. W.: Boston Med. Quart. 8: 1, September, 1957.

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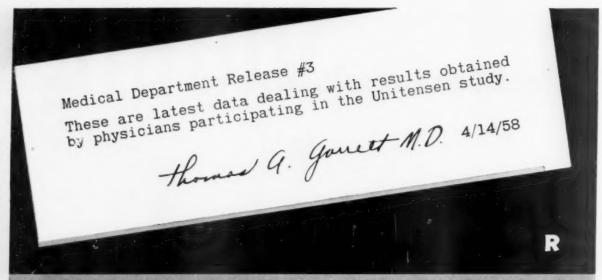
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- ADJUST DOSAGE OF ALL MEDICATION. The patient must be frequently observed and careful adjustment of all agents should be made to determine optimal maintenance dosage.

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No. of Patients	Results	Percent
6,059	Excellent	31.2%
9,987	Good	51.3%
2,441	Fair	12.6%
956	Unsatisfactory	4.9%
594	Side Effects	3.1%

the nationale of proof in practice

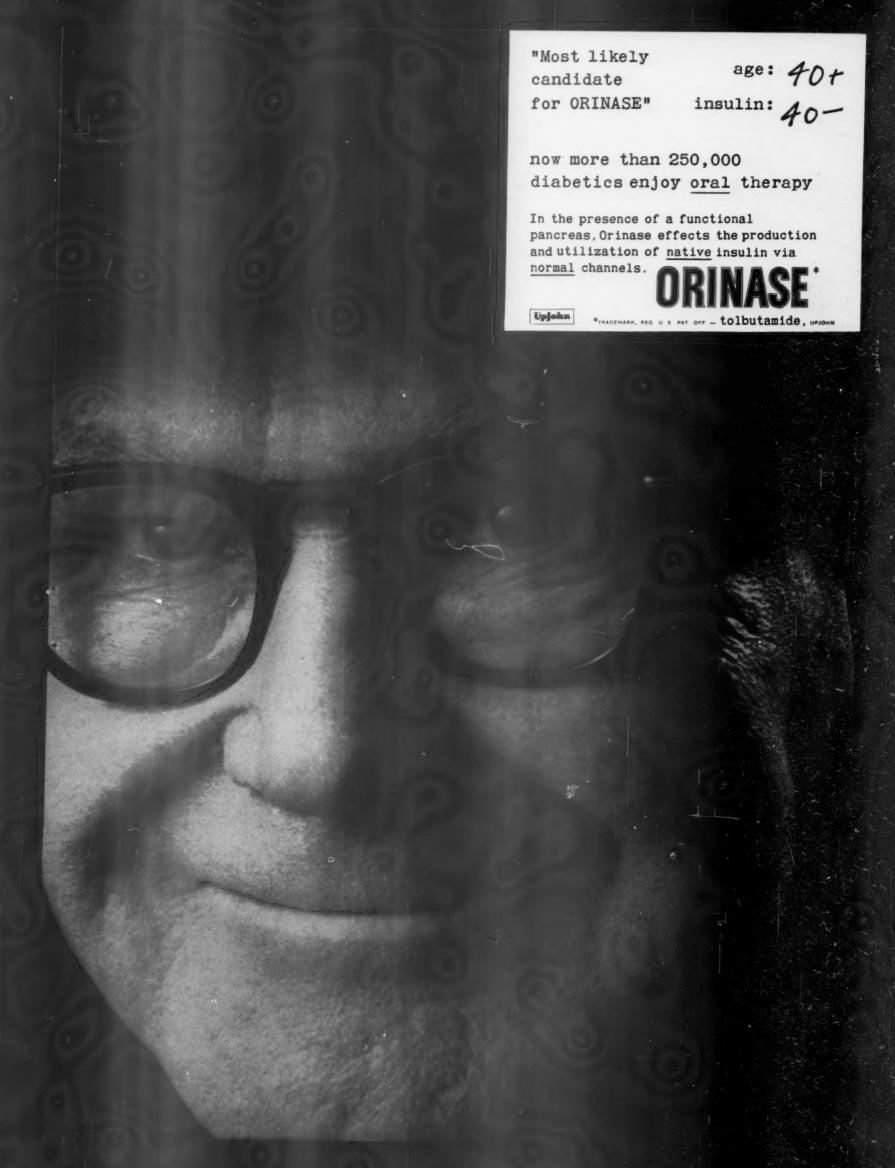
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1. Shalowitz, M.: Geriatrics 11:312, 1956, 2, Warter, P. J.: J. M. Soc. New Jersey 54:7, 1957, 3. Hutcheon, D. E., et al.: Paper presented at Am. Soc. Pharmacol. & Exper. Therap., Nov. 8-10, 1956, French Lick, Ind. 4. Strub, I. H.: To be published, 5. Individual Case Reports to Medical Dept., Pfizer Laboratories.



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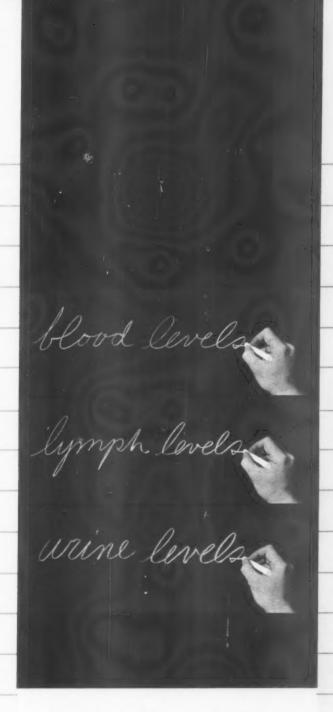
Goldbloom, A. A., Feinstein, M. A. and Eiber, H. B.: Am. J. Dig. Dis., 22:288, 1955.

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References: L. Finele, L. P., and Reyna, L. J.: J. Clin. & Esper. Peychologich, 19:7 (Jan. Mar.) 19:8. 2. Barrabee, P., Wingare, J.: Har Phillips, B. D., and Greenblatt, M.: Postgrad, Med. 19:485 (May) 1955. 2. Kats, E. M., and Kowalienko, Z.: Internat. Rec. Med. 169:596 (Sept.) 1965. 4. Chu, L.: J. Indiana M. A. 29:692 (Ann.) 1957.

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If you listen, you'll learn not only that doctors like "Premarin," but why they like it.

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"Premarin," conjugated estrogens (equine), is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

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## Meat...

### and the Protein Depletion of Severe Infectious Disease

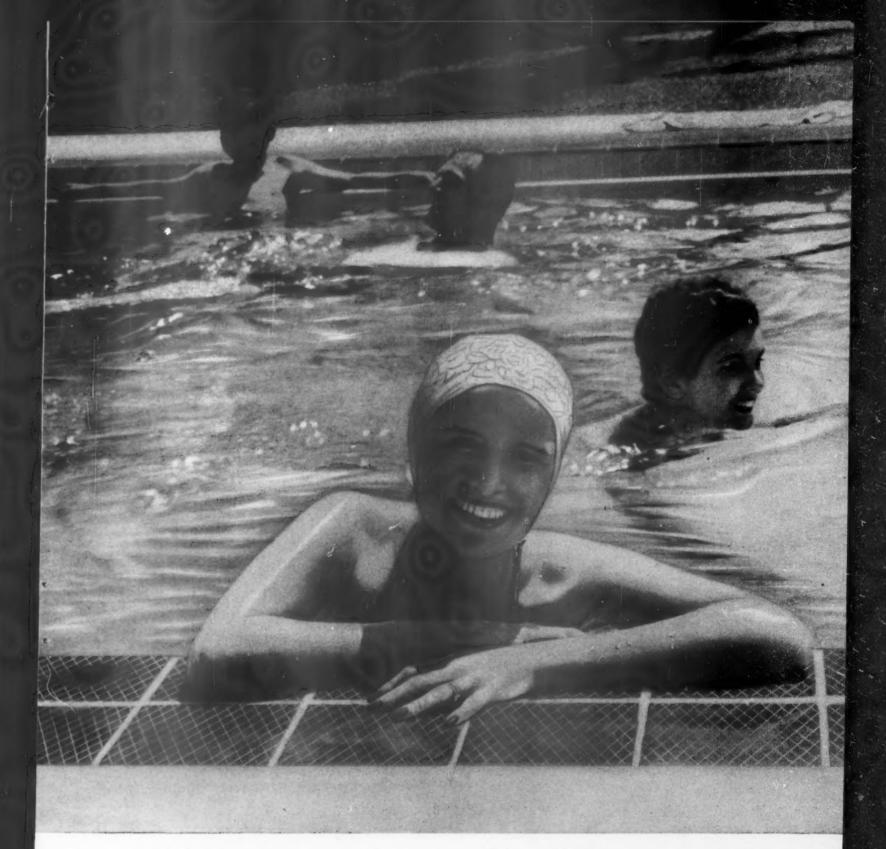
Recovery from severe infectious processes entails more than emergence from the effects of the causative agent. The semistarvation, the inactivity, the suppression of physiologic activity must all be corrected as rapidly and thoroughly as can be tolerated by the patient.

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#### Of course, women like "Premarin"

THERAPY for the menopause syndrome should relieve not only the psychic instability attendant the condition, but the vasomotor instability of estrogen decline as well. Though they would have a hard time explaining it in such medical terms, this is the reason women like "Premarin."

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Proctor, R. C.: Dis. Nerv. Sys. 18:223 1957.
 Feuss, C. D., and Gragg,
 Jr.: Dis. Nerv. Sys. 18:29, 1957.
 Coats, E. A., and Gray, R. W.: Dis. Nerv. Sys. 18:191, 1957.
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mouth.1-3

(1) Settel, E.: J. Am. Geriatrics Soc. 6:39, 1958.
(2) Jefferson, N. C., and Necheles, H.: J. Urol. 76:651, 1956. (3) Necheles, H., and Kirshen, M. M. The Physiologic Basis of Gastrointestinal Therapy, New York, Grune & Stratton, Inc., 1957, p. 87.

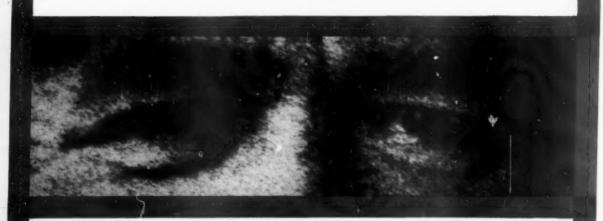
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Source - Hyman, M.: Some Aspects of Psychiatry in General Practice, GP 16:83 (Oct.) 1957.

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\*Bauer, H. G.; Seegers, W.; Krawzoff, M., and McGavack, T. H.: A Clinical Evaluation of Ectylurea (Nostyn®), in press.

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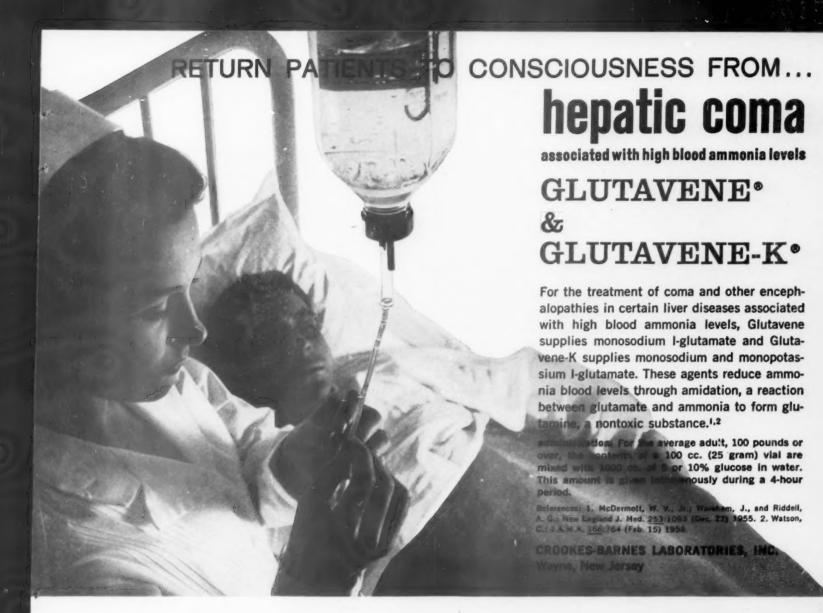
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M. Clin. North America 38:485 (March) 1954.
 J.A.M.A. 162:1031,
 J.A.M.A. 156:680, 1954.
 Yale J. Biol. & Med. 28:308, 1955/56.





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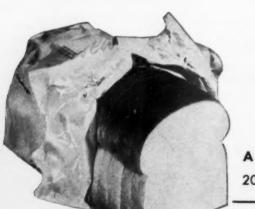
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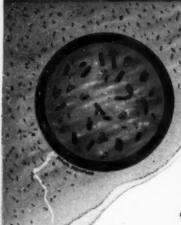
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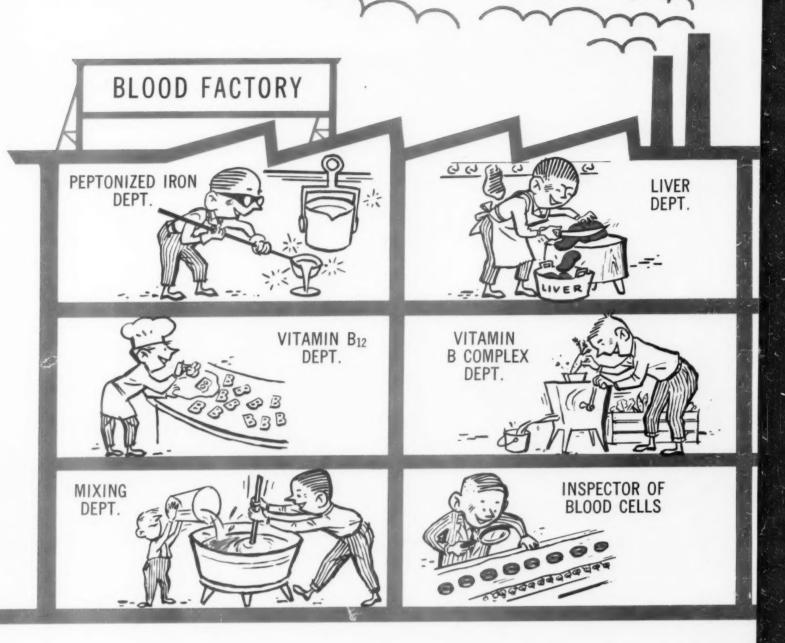
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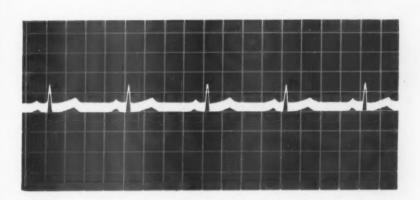
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1. Aravanis, C., and Luisada, A. A.: Am. J. Cardiology, in press.

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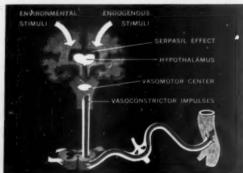
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Adapted from Moyer, J. H., Dennis, E., and Ford, R.: Arch. Int. Med. 96:530 (Oct.) 1955.

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1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc. 234: 150, Aug. 1957.

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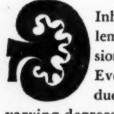
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\*Judson, W. E., Hollander, W., and Wilkins,

R. W.: Circulation 13:664 (May) 1956.

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